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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 917 Pacific Ave #600 Tacoma, WA 98402
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13. SUPPLEMENTARY NOTES

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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1. **INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

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 antiandrogens 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:** *Provide a brief list of keywords (limit to 20 words).*

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

3. **ACCOMPLISHMENTS:** *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

What were the major goals of the project?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

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	12-36 months	75%

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	12-36 months	75%

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	12-36 months	25%

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
Validate Hsp40/70 inhibitors re-sensitize resistant CRPC cells and tumors to enzalutamide and/or abiraterone	1-18 months	12-36 months	85%

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

Milestones	target dates	actual dates	%completion
Identify one or more mechanisms by which Hsp40 and/or Hsp70 inhibitors re-sensitize resistant CRPC cells to enzalutamide and/or abiraterone.	6-18 months	12-36 months	80%

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
Identify synergy between chaperone inhibitors and selected metabolic inhibitors; identify metabolic pathways, whose inhibition (alone or combined with chaperone inhibition) re-sensitizes resistant CRPC to enzalutamide and/or abiraterone; validate non-invasive HP-MRSI to predict treatment efficacy *in vivo*.	12-36 months	12-36 months	70%

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?
For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

Specific Aim 1: The goal of Specific Aim 1 is to advance the development of clinical candidates targeting Hsp70 and Hsp40. In earlier funding cycles, we focused on target validation and compound selectivity. Recent hit-to-lead work 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). Our collaborator, Prof. Gestwicki, has developed a number of additional Hsp70 inhibitors, based on the JG platform, and we will evaluate them both in vitro and in vivo for efficacy in CRPC models used in this award. Unfortunately, further development of Hsp40 inhibitors based on the C86 platform has been lagging. To remedy this situation, we added Dr. Yeong Sang Kim, a medicinal chemist and former postdoctoral fellow of our collaborator on this award, Jane Trepel, as a part-time contractor to provide his expertise in the design of novel C86 derivatives for synthesis and in vitro/in vivo testing. Dr. Kim has provided 10-15 novel structures to us for synthesis at mg amounts by a pharmaceutical CRO. Included in the novel set of C86 derivatives are compounds expected to localize to the mitochondria (see rationale below), which is a natural characteristic of JG-98. We will pursue these studies during the next cycle.

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 re-sensitize resistant CRPC to enzalutamide and/or abiraterone. In a previous publication (Moses MA, et al. Cancer Res. 2018) 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 last cycle, we confirmed and expanded on these findings using the Incucyte instrument which supports multi-concentration 6-day analysis of cell growth that can be monitored in real time. Although further *in vivo* corroboration of these data was delayed due to the Covid-19 pandemic, we have made significant progress on this front during the current cycle (see Fig. 1). The *in vivo* data below corroborate and support our *in vitro* findings.

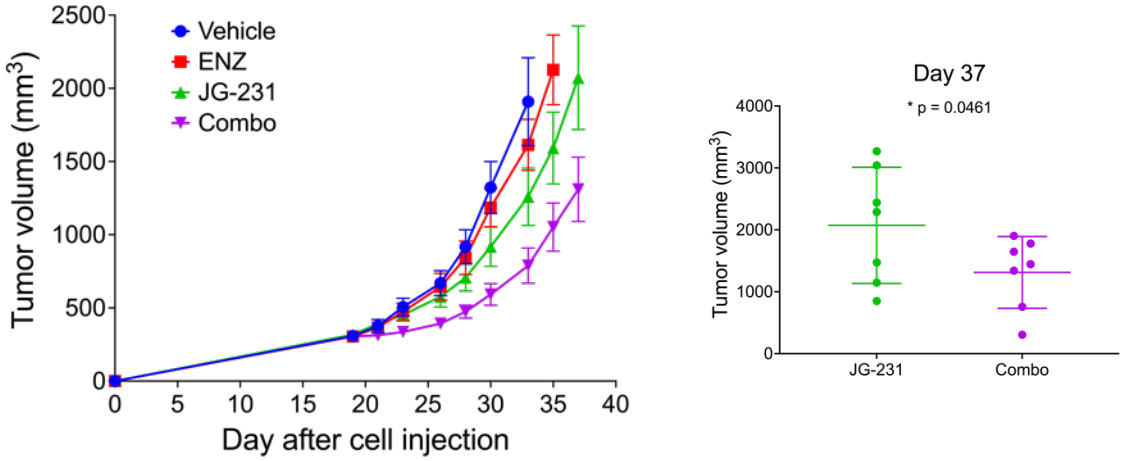
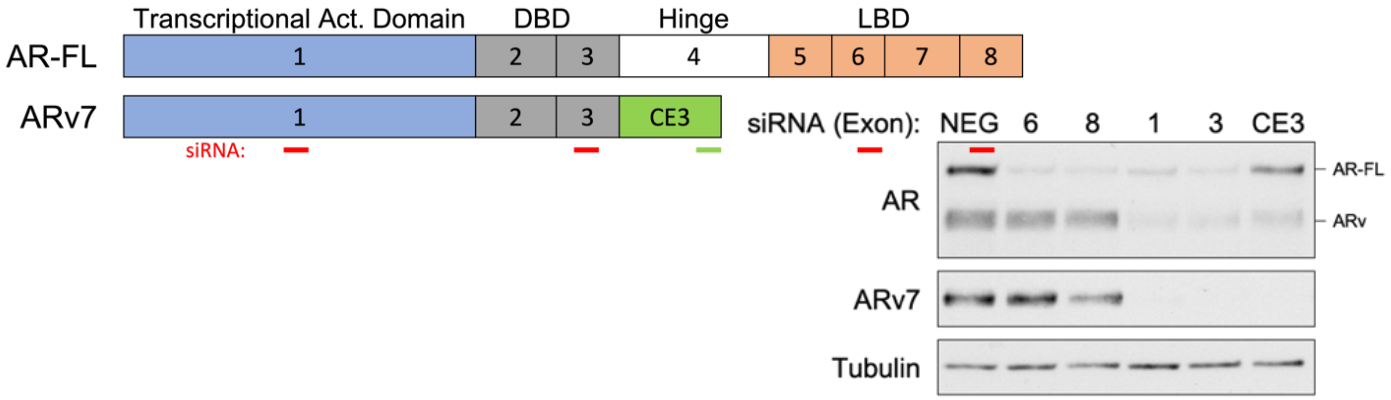


Fig. 1. Left panel: Mean tumor volume (+/- SEM) of 22Rv1 xenografts in mice treated with vehicle (n=7), JG-231 (6 mg/kg; n=7), enzalutamide (ENZ) (25 mg/kg; n=7), or combo (n=7). Right panel: Mean tumor volume (+/- SD) of 22Rv1 xenografts in mice treated with vehicle, JG-231, Enzalutamide, or the combination at day 37 (post 22Rv1 cell inoculation).

One of the goals of **Specific Aim 2** is to understand the mechanistic basis of re-sensitization to ADT by these chaperone inhibitors, in particular JG-98. In Moses et al. (Cancer Res, 2018) we proposed that chaperone inhibitor-stimulated androgen receptor degradation was the mechanism underlying the activity of JG-98. During the last cycle, we showed that that JG-98promotes a reduction in mitochondrial Oxidative Phosphorylation (OxPhos), the preferred energy pathway of CRPC cells, while simultaneously increasing a shift to glycolysis, the preferred energy pathway of normal prostatic epithelium. Under these altered metabolic conditions, re-sensitization to androgen deprivation therapy occurs. Unexpectedly, and of significant interest, CRPC sensitivity to JG-98 was not impacted by siRNA knockdown of either full-length androgen receptor or Arv7, the constitutively active androgen-independent androgen receptor splice variant (see Fig. 2).



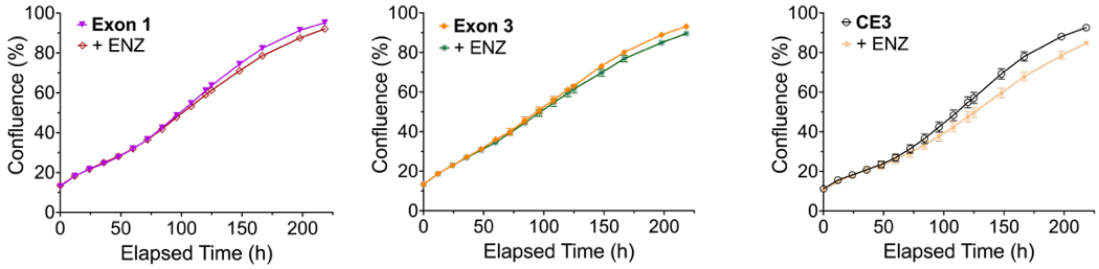


Fig. 2. JG-98 sensitizes 22Rv1 to ADT treatment independent of impact on androgen receptor. Top panel, previous page: Map of siRNA complementarity. Bottom panel, previous page: western blot analysis of 22Rv1 lysate transfected with respective siRNAs 24 h post-transfection. This page, top: Incucyte growth analysis of 22Rv1 measuring AR-KD impact on enzalutamide sensitivity.

These data suggest an alternative mechanism underlying the activity of JG-98 in CRPC as a single agent with the ability to re-sensitize to ADT. In the previous cycle, we also reported that brief treatment with JG-98 not only changed the energy profile of CRPC cells but also caused rapid loss of a majority of large and small ribosomal subunits destined for translocation into the mitochondrial matrix for assembly of the mitoribosome. Since the single mitoribosome translates only 13 proteins, all of which are subunits of the various protein complexes that comprise the electron transport chain (ETC), we used click chemistry to examine the impact of JG-98 on mitochondrial protein synthesis (see Fig. 3).

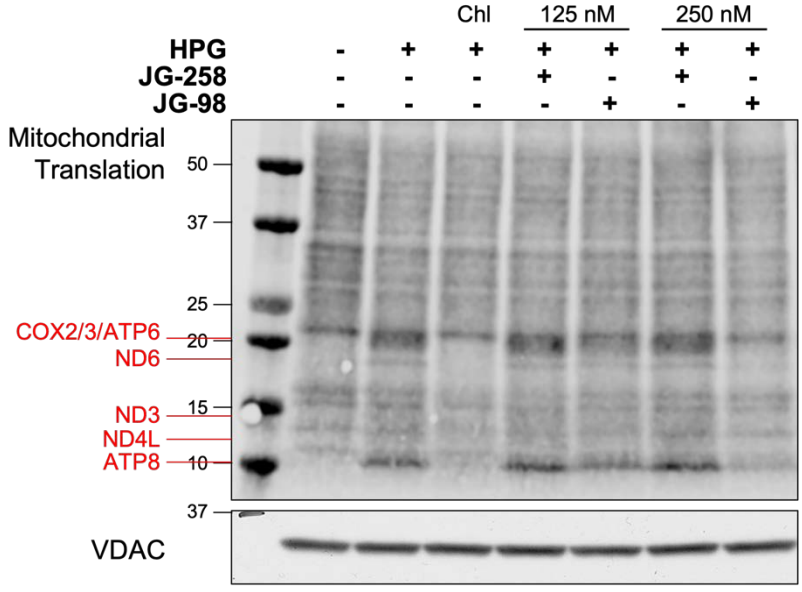


Fig. 3. Mitochondrial translation assay using mitochondria isolated from 22Rv1 cells treated with 125 or 250 nM JG-98 or inactive analog (JG-258) for 24 hours. (top panel) detection of HPG incorporation into mitochondrial protein synthesis. (bottom panel) western blot detection of VDAC (load control). Chl, chloramphenicol, is a specific inhibitor of mitochondrial protein synthesis. The labels in red identify ETC subunits synthesized in mitochondria whose translation is inhibited by JG-98.

Thus, it appears that JG-98 impacts CRPC growth and re-sensitizes the cells to ADT as a consequence of OxPhos inhibition due to failure of JG-98 treated cells to fully assemble a functional ETC. These findings also identify the mitochondrial Hsp70 – HspA9 – as an important contributor to assembly and/or stability of the mitoribosome. These findings will be pursued further during the upcoming cycle.

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 previous cycles, 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 using these inhibitors. Given our novel and unexpected findings during the current cycle that JG-98 indirectly inhibits functional assembly of the ETC, we wished to provide confirmatory orthogonal data. 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 ETC, resulting in oxidative phosphorylation and ATP synthesis. In the previous cycle, we used the Incucyte instrument to confirm that 22Rv1 CRPC cells are growth inhibited by low concentrations of IACS. Further, we found that complex I inhibition is able to re-sensitize these cells to enzalutamide *in vitro* and that JG-98 and IACS synergize *in vitro* to inhibit CRPC growth. In the current cycle, we have obtained confirmatory *in vivo* data to support our previous *in vitro* findings (see Fig. 4).

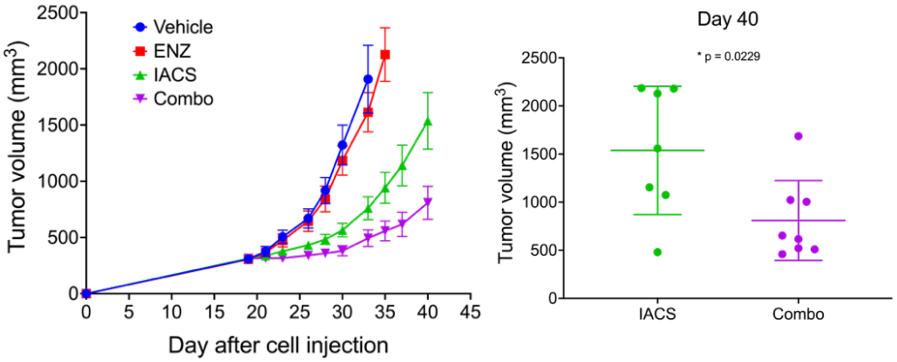


Fig. 4. Left: 22Rv1 xenograft growth represented as mean tumor volume +/- SEM in mice treated with vehicle (n=7), enzalutamide (25 mg/kg; n=7), IACS (7.5 mg/kg; n=7), or combo (n=8). Right: Mean tumor volume +/- SD in mice treated with IACS or combo at day 40 post 22Rv1 cell inoculation.

Taken together, the data we have obtained during the current cycle strongly suggest that disruption of mitochondrial metabolism may be sufficient to re-sensitize to ADT while also displaying potent single agent activity in CRPC. We will explore this possibility further in the current cycle. An additional milestone of Major Task 6/SA3 is to validate non-invasive imaging using hyperpolarized magnetic resonance spectroscopy (HP-MRSI) as a useful tool able to predict treatment efficacy *in vivo*. In our initial experiments performed during the current cycle we have used hyperpolarized [1-^{13}C]pyruvate and followed its conversion to [1-^{13}C]lactate or [1-^{13}C]bicarbonate (following pyruvate decarboxylation and entry into the TCA cycle) to assess rates of glycolysis and OxPhos (see Fig. 5).

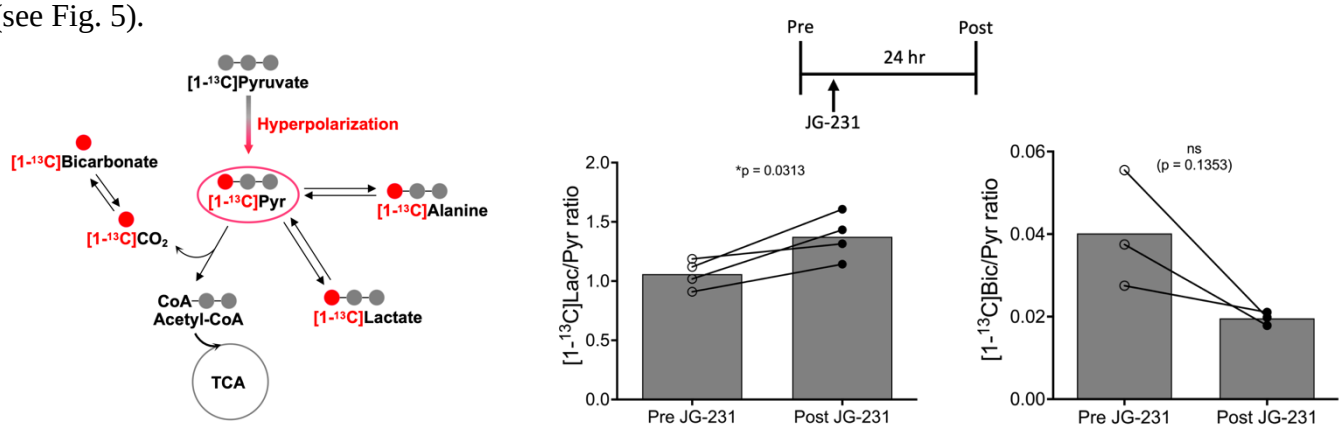


Fig. 5. Left panel: Diagram of detectable metabolic conversion pathways of [1-^{13}C] pyruvate. Middle and Right panels: HP-MRS imaging of 22Rv1 xenografts. Middle: Ratio of [1-^{13}C]lactate to [1-^{13}C]pyruvate indicates increased tumor glycolysis 24 h after JG-231 administration to mice; Right: Ratio of [1-^{13}C]Bic to [1-^{13}C]pyruvate indicates decreased TCA cycle activity at the same timepoint. Bic = bicarbonate.

This non-invasive imaging methodology will be further explored in the current cycle and additional hyperpolarized metabolites will be evaluated for their utility in reporting on the metabolic preferences of CRPC and their disruption.

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Arnav Sinha joined the project as a new Post-Bac Fellow in the Neckers lab. He is being mentored by Frank Echtenkamp, a Staff Scientist in the Neckers lab, to develop research skills related to the studies described in the SOW, Specific Aims 2 and 3. Arnav is also able to take relevant courses at the FAES Graduate School, which are offered to him at no cost. He is encouraged to attend seminars, workshops and conferences related to his work. Genesis Rivera-Marquez continues as a Geneva Foundation employee and works on this project as a collaborator. She 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. Both Genesis and Arnav will be co-authors on a manuscript currently in preparation.

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Publication and presentation at relevant scientific meetings.

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

We will submit at least one, and perhaps two, manuscripts for publication that describe our findings and delve deeper into the role of mitochondrial Hsp70 in protein quality control in mitochondria and requirement for mitoribosome assembly/stability. We will pursue the hypothesis that this represents a novel vulnerability of CRPC. We will also devote a greater effort to focusing on Hsp40 inhibition as discussed in SA1, particularly whether targeting a C86 derivative to the mitochondria improves its efficacy in CRPC independent of its role in stabilizing androgen receptor.

4. **IMPACT:** D*escribe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

We identified a unique metabolic vulnerability of CRPC cells to inhibitors of the ETC and we showed synergy with the Hsp70 inhibitor JG-98. We also uncovered an impact of JG-98 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 as mitochondrial protein translation is inhibited, leading to incomplete assembly of ETC complexes. This in turn is accompanied by re-sensitization to ADT treatment.

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to Report

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to Report

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Nothing to Report

5. **CHANGES/PROBLEMS:** *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*

Nothing to Report

Changes in approach and reasons for change
Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

Nothing to Report

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

Nothing to Report

Changes that had a significant impact on expenditures
Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Nothing to Report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

Nothing to Report

Significant changes in use or care of vertebrate animals

Nothing to Report

Significant changes in use of biohazards and/or select agents

Nothing to Report

6. PRODUCTS: *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

  Arielle Shkedi, Michael Adkisson, Andrew Schroeder, Walter L Eckalbar, Szu-Yu Kuo, Leonard Neckers, and Jason E. Gestwicki. Inhibitor Combinations Reveal Wiring of the Proteostasis Network in Prostate Cancer Cells. J. Med. Chem. 2021, 64, 14809–14821. (publication status: published; federal support acknowledged)

  Arielle Shkedi, Isabelle R. Taylor, Frank Echtenkamp, Poornima Ramkumar, Mohamed Alshalalfa, Genesis M. Rivera-Marquez, Michael A. Moses, Hao Shao, Robert Jeffrey Karnes, Len Neckers, Felix Feng, Martin Kampmann, and Jason E. Gestwicki. Selective vulnerabilities in the proteostasis network of castration-resistant prostate cancer. Cell Chemical Biology. 2022, 29, 490–501.
  (publication status: published; federal support acknowledged)

  Frank J. Echtenkamp, Ryo Ishida, Genesis M. Rivera-Marquez, Marisa Maisiak, Oleta T. Johnson, Jonathan H. Shrimp, Steve Ralph, Ian Nisbet, Matthew D. Hall, Jason E. Gestwicki, Leonard M. Neckers. Mitoribosome Sensitivity to Hsp70 Inhibition Uncovers Metabolic Liabilities of CRPC and Re-sensitizes to Androgen Deprivation Therapies.
  (publication status: in preparation; federal support acknowledged)

  Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to Report

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

Presentation at Cell Stress Society International Virtual Meeting, September 2022: Targeting mitochondrial Hsp70 and the ETC: A unique vulnerability in prostate cancer.

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

  Nothing to Report

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

  Nothing to Report

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

  Nothing to Report

- **Other Products**
  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:
  - *data or databases;*
  - *physical collections;*
  - *audio or video products;*
  - *software;*
  - *models;*
  - *educational aids or curricula;*
  - *instruments or equipment;*
  - *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*

- *clinical interventions;*
- *new business creation; and*
- *other.*

Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?
Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change".

Example:

Name:	*Mary Smith*
Project Role:	*Graduate Student*
Researcher Identifier (e.g. ORCID ID):	*1234567*
Nearest person month worked:	*5*
Contribution to Project:	*Ms. Smith has performed work in the area of combined error-control and constrained coding.*
Funding Support:	*The Ford Foundation (Complete only if the funding support is provided from other than this award.)*

Jason Gestwicki: No Change

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Nothing to Report

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to* ***https://ebrap.org/eBRAP/public/index.htm*** *for each unique award.*

AWARD CHART: Attached

9. APPENDICES: *Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.*