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14. ABSTRACT

The clinical potential of PARP-1 inhibitors has been increasingly recognized over the last years. The therapeutic utility of known PARP-1 inhibitors has been limited by their non-specific activity. All conventional PARP-1 inhibitors have been designed as NAD-mimetics. Therefore, such compounds also inhibit other enzymes that use NAD, producing various off-target effects. To address these limitations, we have developed a novel class of PARP-1 inhibitors by targeting the histone-dependent route of PARP-1 activation, a mechanism that is unique to PARP-1. During the reported period we synthesized and tested a panel of novel PARP-1 inhibitors. Several compounds demonstrated prominent antitumor activities. However, their ADME and pharmacokinetic properties were suboptimal. We are currently undertaking medicinal chemistry optimization approach to create novel chemical probes with improved functional characteristics. We anticipate that our experiments will identify potential recurrence/progression biomarkers of PC.

15. SUBJECT TERMS

PARP-1, PARG, PARP-1 inhibitors, histone-dependent PARP-1 regulation, poly(ADP-ribose), prostate cancer cells

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1. INTRODUCTION:

Androgen ablation has been the mainstay treatment for advanced prostate cancer (PC). Importantly, androgen receptor (AR) signaling is vital not only for the initiation of PC, which is initially androgen-dependent, but also for castration-resistant disease. However, AR-mediated functions are not completely abrogated by existing androgen deprivation therapies (ADT) and their therapeutic failure is often accompanied by various molecular alterations, such as androgen-independent AR activation and AR structural alterations, including expression of constitutively active AR variants that lack the ligand-binding domain (AR-Vs). PARP-1 serves as a functional modulator of AR transcriptional activity. Our proprietary histone-dependent PARP-1 inhibitors suppress AR transcriptional function and are therefore effective against both androgen-dependent and -independent routes of AR activation. Our studies show that our lead histone-dependent PARP-1 inhibitor 5F02 demonstrates superior antitumor activity compared with clinically relevant NAD-like PARP-1 inhibitors and antiandrogen agents in both androgen-dependent and castration-resistant cell models of human PC. The overall objective of our proposal is to examine the therapeutic potential of histone-dependent PARP-1 inhibitors and to investigate the molecular mechanisms underlying their antitumor activity. The proposed studies will provide valuable insight into new avenues for potential treatment of advanced prostate cancer.

2. KEYWORDS: PARP-1, PARG, PARP-1 inhibitors, histone-dependent PARP-1 regulation, poly(ADP-ribose), prostate cancer cells

3. ACCOMPLISHMENTS:

What were the major goals of the project?

To Specific Aim 1: 1) Examine the in vitro antitumor activity of histone-dependent PARP-1 inhibitors using androgen-dependent and castration-resistant PC cell lines. The antitumor activity of a lead group of seven histone-dependent PARP-1 inhibitors will be tested using LNCaP, PC-3 and DU-145 cells. AR transcriptional activity, poly(ADP-ribose) expression, proliferation and apoptosis will be examined. 2) Examine the effect of histone-dependent PARP-1 inhibitors on androgen-dependent and -independent activation of AR signaling LNCaP cells will be pretreated with histone-dependent PARP-1 inhibitors, followed by stimulation with the synthetic androgen agonist R1881, or non-androgen ligands IL-6, IL-8 and IGF-1. 3) To determine the role of mutations in DNA damage-repair genes for sensitivity of PC cells to histone-dependent PARP-1 inhibitors. The proposed studies will address the causal role of the mutations in DNA-repair genes for sensitivity of PC cells to histone-dependent PARP-1 inhibitors. These studies will be performed using parental (PTEN-negative) and PTEN-expressing PC-3 cells. 4) To perform physicochemical and ADME analysis of histone-dependent PARP-1 inhibitors. These studies will be performed in collaboration with the Moulder Center for Drug Discovery Research.

To Specific Aim 2: 1) To investigate the role of PARP-1 localization in the promoters of NF-kappaB-dependent pro-tumorigenic genes. We will pinpoint the position of PARP-1 in promoters of these genes. 2) To determine the effects of PARP-1 and PARG dysregulation during the onset of PC. We will knock down PARP-1 by expressing anti-PARP-1 shRNA in PC cells. Upon treatment with shRNA, we will monitor the expression of NF-kappa B-dependent genes.

What was accomplished under these goals?

We have now investigated the antitumor activity of histone-dependent PARP-1 inhibitors against androgen-dependent and castration-resistant PC cells, as proposed in the statement of work. We have made significant progress in the first aim of the proposal. The results we obtained in the past year are consistent with our hypothesis and reinforce our experimental rationale. Specific progress is reported below.

Specific Aim 1:

To Task 1. Examine the in vitro antitumor activity of histone-dependent PARP-1 inhibitors using androgen-dependent and castration-resistant PC cell lines. In our previous studies we performed analysis of 50,000 small compounds, selecting positive hits that reduced PARP-1 activity by at least 3-fold. Based on anti-PARP-1 activity, structural analysis, and ease of synthesis we ultimately selected the lead compound 5F02 for future studies. 5F02 demonstrated superior ability to inhibit growth of tumor cells both in cell and animal models of human PC when compared with classical PARP-1 inhibitor olaparib. We synthesized sixteen 5F02 analogs in

which the ester and quaternary ammonium salt have been altered to amide and/or desmethyl modifications respectively to improve stability of 5F02 (**Fig.1**).

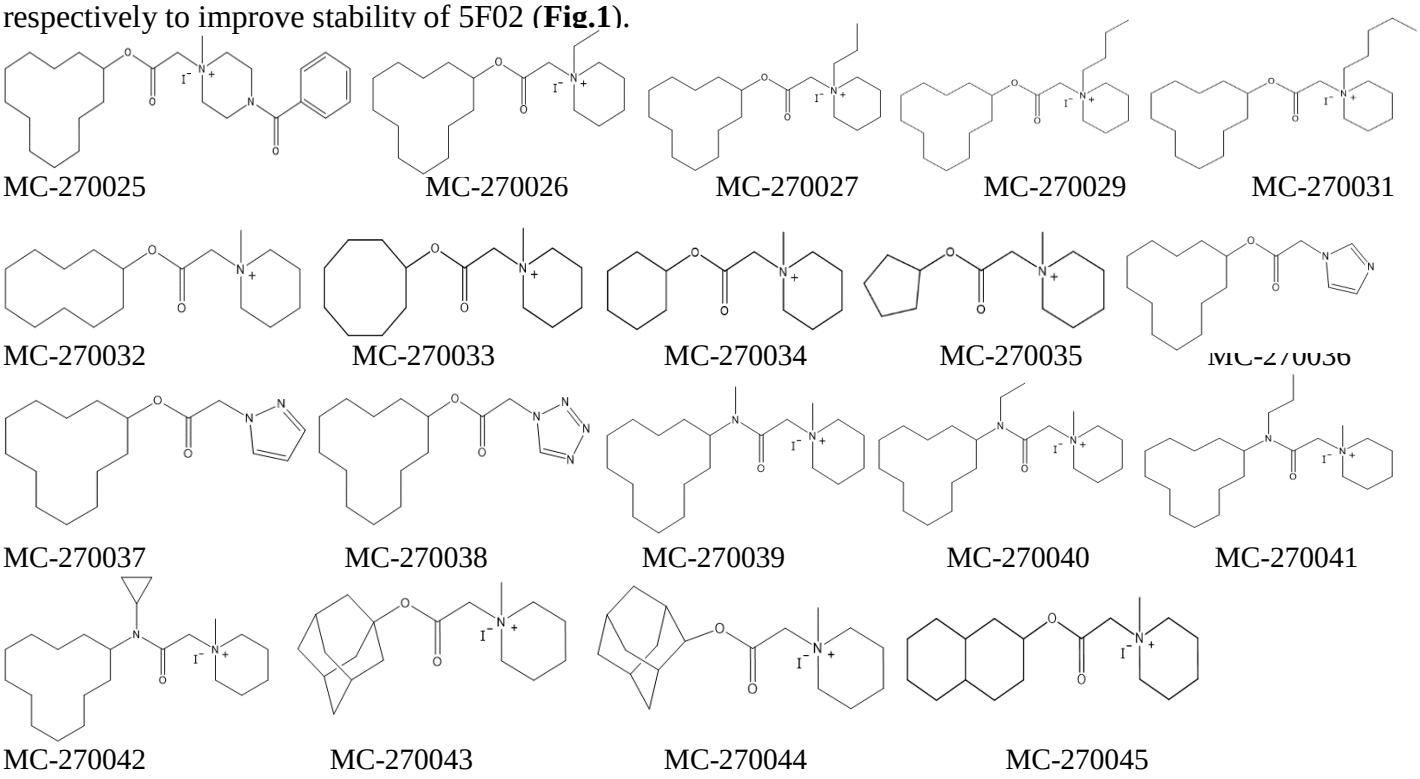

Figure 1. Novel analogs of 5F02.

To Task 4: To perform physicochemical and ADME analysis of histone-dependent PARP-1 inhibitors. We analyzed physicochemical and ADME (Absorption, Distribution, Metabolism, and Excretion) properties of histone-dependent PARP-1 inhibitors. These parameters need to be analyzed and studied to provide basic information about the properties of new probe and tool compounds prior to their entry into expensive and time-consuming animal studies. First, we examined the metabolic stability of 5F02 in liver microsomes of different species including human, rat, and mouse. These experiments were performed by our co-Investigator John Gordon, Ph.D. at the Moulder Center for Drug Discovery Research at Temple University School of Pharmacy. The results of these experiments are presented in **Table 1.**

To Tasks 1-3. Synthesis and testing of novel histone-dependent PARP-1 inhibitors. As it was indicated in our previous report, despite their promising antitumor profile, our lead non-NAD-like PARP-1 inhibitors 5F02 and MC-270022 demonstrated suboptimal ADME (Absorption, Distribution, Metabolism, and Excretion) and PK (pharmacokinetic) properties. In pursuit of identifying PARP-1 inhibitors with superior anti-tumor activity and improved ADME and PK properties, we selected a collection of seven novel 5F02 derivatives using medicinal chemistry diversification approach (**Fig.1**). FDA-approved NAD-like PARP-1 inhibitors olaparib, veliparib, and rucaparib were used as reference compounds in these studies (**Fig.2**). As demonstrated in **Figure 3**, MC-270029 and MC-270031 probes suppressed viability of androgen-dependent LNCaP and castration-resistant PC-3 and DU-145 prostate cancer cells with higher efficacy when compared with other 5F02 analogs. The activity of MC-270029 and MC-270031 was comparable to that of clinically approved NAD-like PARP-1 inhibitors **(Fig.2 and 3)**.

Next, we examined the anti-PARP-1 activity of MC-270029 and MC-270031 by evaluating their effect on H2O2-induced expression of Poly(ADP-ribose) (pADPr), a marker of PARP-1 activity. Unexpectedly, treatment with both agents failed to inhibit H2O2-induced pADPr expression. NAD-like PARP-1 inhibitors olaparib, veliparib, rucapariob, and talazoparib were used as positive controls in this experiment. We are currently undertaking medicinal chemistry optimization approach to create novel chemical probes with improved anti-PARP-1 activity. In collaboration with the Moulder Center for Drug Discovery Research at Temple University School of Pharmacy, we will synthesize novel non-NAD-like PARP-1 inhibitors and test their anti-PARP-1 and antitumor activities using functional (cell viability, apoptosis), immunological (western blotting, ELISA) and

molecular biology (qPCR) assays. We also plan to examine ADME and PK characteristics of novel agents and evaluate their *in vivo* antitumor activities as described in the Statement of Work.

Table 1. In vitro assessment of ADME properties during lead selection and lead optimization. MLM = Mouse liver microsomes; HLM = Human liver microsomes.

MC-number	IC50, H4/PARP 1 (nM)	Max. Aq. Solubility (uM)	t1/2, MLM (+ NADPH) (min)	% remaining @ 60 min, MLM (- NADPH)	t1/2, HLM (+ NADPH) (min)	% remaining @ 60 min, HLM, (- NADPH)
MC-270025	29.2	200	8	84%	< 2	107%
MC-270026	174	200	4.7	96%	3.4	88%
MC-270027	142	194	8.9	100%	< 2	87%
MC-270029	136	186	16.2	89%	< 2	100%
MC-270031	258	196	16.0	70%	< 2	100%
MC-270032	53.7	181	6.2	99%	7.7	100%
MC-270033	80	182	2.2	97%	> 60	95%
MC-270034	77.1	187	2.9	101%	> 60	97%
MC-270035	57.1	200	21.2	97%	> 60	90%
MC-270036	> 10,000	49.3	2.4	7%	NA	NA
MC-270037	> 10,000	34.8	< 2	3%	NA	NA
MC-270038	> 10,000	21.9	< 2	2%	NA	NA
MC-270039	191	200	5.5	98%	< 2	88%
MC-270040	48.5	200	6.1	102%	NA	NA
MC-270041	41	200	6.4	95%	NA	NA
MC-270042	63.1	200	15.2	104%	NA	NA
MC-270043	88.4	181	< 2	107%	NA	NA
MC-270044	107.8	188	4	101%	NA	NA
MC-270045	54.6	174	< 2	100%	NA	NA

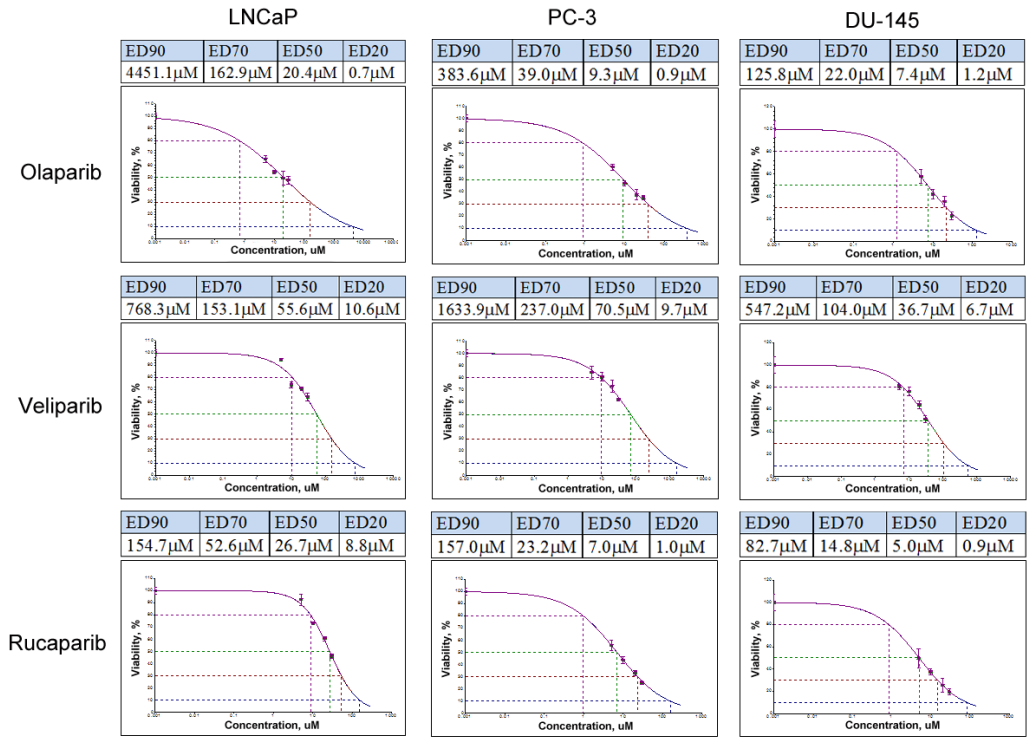

Figure 2. The effect of clinically approved NAD-like PARP-1 inhibitors on viability of androgen-dependent LNCaP and castration-resistant PC-3 and DU-145 prostate cancer cells. The cells were treated with escalating concentrations of PARP-1 inhibitors for 72 hrs. Cellular viability was assessed using the CellTiter Blue assay. The effective doses (ED) were calculated using XLfit software.

Our facilities at UND and the facilities of our collaborators at the Fox Chase Cancer Center and Temple University School of Pharmacy have either been closed or their work has been restricted due to COVID-19 for a substantial amount of time this year. There have been restrictions on hours and the amount of people that could work on the project both in the lab and at the collaborating facilities. Companies that provide reagents and supplies have also been experiencing similar restrictions; which, have affected the speed of the work being done. Due to these restrictions our progress has been somewhat slowed.

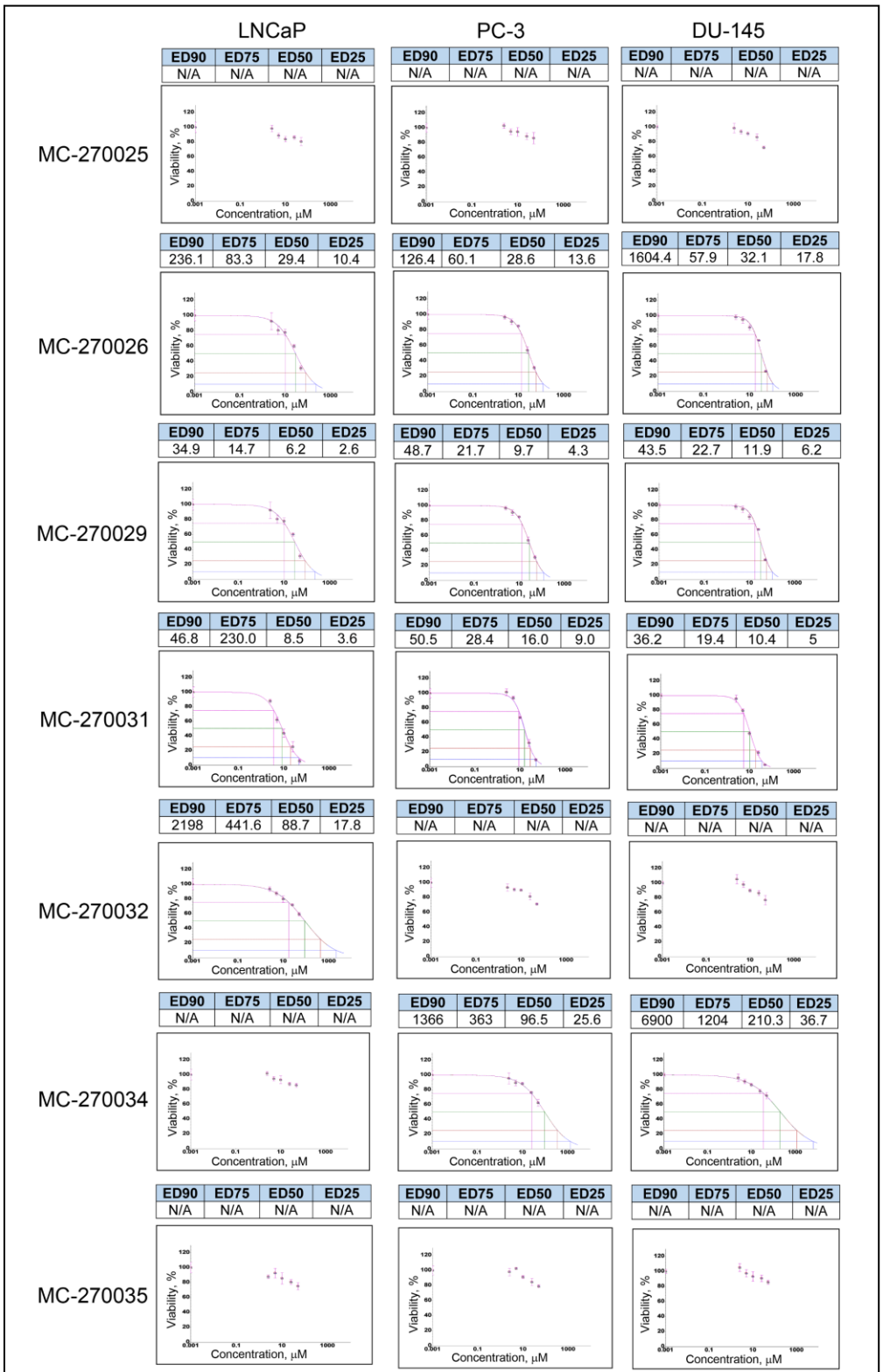

Figure 3. The effect of novel non-NAD-like PARP-1 inhibitors on viability of androgen-dependent LNCaP and castration-resistant PC-3 and DU-145 prostate cancer cells. The cells were treated with escalating concentrations of PARP-1 inhibitors for 72 hrs. Cellular viability was assessed using the CellTiter Blue assay. The effective doses (ED) were calculated using XLfit software. N/A - Non Accessible.

Specific Aim 2: To investigate the molecular mechanism underlying PARP-1-dependent control of PC malignant growth.

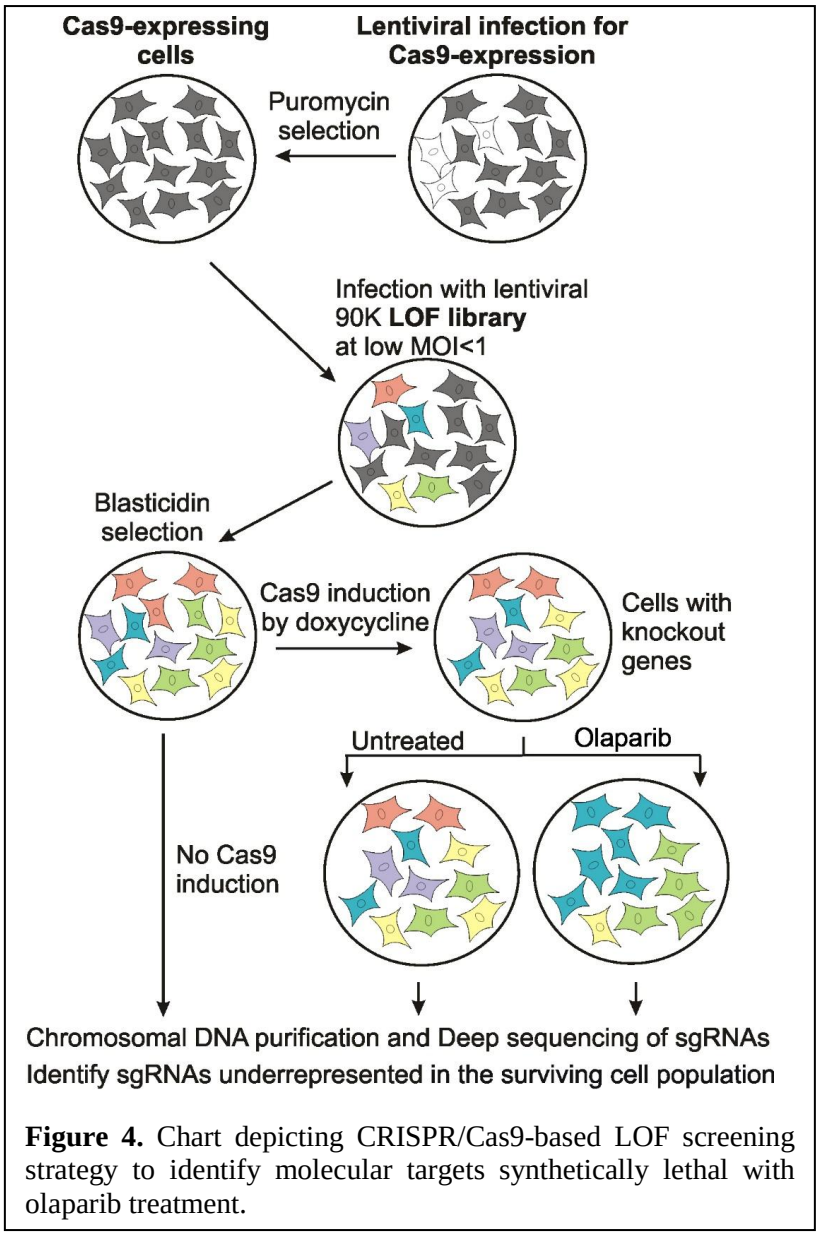

Figure 4. Chart depicting CRISPR/Cas9-based LOF screening strategy to identify molecular targets synthetically lethal with olaparib treatment.

Synthetic lethality screens hold great promise for the development of novel therapeutic interventions. Synthetically lethal interactions may provide more druggable targets than individual cellular factors. For example, although only about 1,000 genes in S. cerevisiae are individually essential for growth, about 10,000 of digenic interactions between non-essential mutations result in synthetic lethality. We have applied CRISPR/Cas9-based high-throughput loss-of-function (LOF) screening to identify genes involved in the resistance to PARP-1 inhibitors. Initially, the experiments were performed using clinically approved PARP-1 inhibitor olaparib. A brief overview of this strategy is depicted in **Fig4.** We have characterized our library-transformed LNCaP prostate cancer cell line and optimized the hit selection parameters using a previously established gold standard set of essential and non-essential genes. Next, androgen-dependent LNCaP prostate cancer cells were incubated with olaparib at 10 μM for 15 days (about six passages). We anticipated that during this time the cells with those knockout genes, which contribute to the resistance to olaparib would be eliminated from the cell population. In opposite, the cells with those knockout genes, which contribute to the sensitivity to olaparib would be enhanced in the cell population. Next, we identified under- and over-represented sgRNAs and their corresponding gene targets in the surviving cell population. The primers corresponding to sequences flanking the guide in the lentiviral vector included 8-bp bar codes for Illumina-based sequencing. Thus, each sgRNA served as an individual DNA barcode that was used to count the number of cells carrying guides by sequencing. Based on the highest rank of identified hits, we have chosen to focus on the genes, which have not been previously reported to be involved in olaparib resistance **(Table 2)**. We plan to assess the druggability of the identified synthetically lethal targets. These studies will address the following questions: 1) What are the molecular mechanisms addressed by the targets? PubMed, GeneCards, and String databases will be searched to determine mechanisms addressed by the targets, characterize their up- and downstream effectors and expression levels at different stages of ccRCC; 2) Are (or were ever) there any known drugs for these targets in clinical trials for any indication? DrugBank, clinicaltrials.gov, and TTD databases will be used to conduct the search; 3) Are there any known chemical inhibitors for these targets? GeneCards, ChEMBL, ChEBI, DrugBank, STITCH, canSAR and BindingDB databases will be searched to identify potential inhibitors and determine 3D-structure-based druggability. Our studies also suggest that overexpression or activation of some genes may sensitize prostate cancer cells to olaparib **(Table 2)**. Therefore, we also plan to investigate if activation of these gene products may augment the antitumor activity of olaparib.

Gene symbol	Product	Cellular function
FERMT1	Fermitin family member 1	The encoded protein is involved in integrin signaling and linkage of the actin cytoskeleton to the extracellular matrix.
IL20	Interleukin 20	The protein encoded by this gene is a cytokine structurally related to interleukin 10. Among its related pathways are PEDF-induced signaling and Akt signaling.
ALPL	Alkaline phosphatase	The product of this gene is a membrane bound glycosylated enzyme that is not expressed in any particular tissue and is, therefore, referred to as the tissue-nonspecific form of the enzyme.
BICDL2	BICD Family Like Cargo Adaptor 2	BICDL2 is predicted to function as a linker between secretory vesicles and microtubule motor proteins.
TMEM260	Transmembrane Protein 260	Encodes a transmembrane protein of unknown function.
OR4N2	Olfactory Receptor Family 4 Subfamily N Member 2	High expression of OR4N2 is associated with increased mortality in stomach adenocarcinoma.
ELF4	E74 Like ETS Transcription Factor 4	The protein encoded by this gene is a transcriptional activator that binds and activates the promoters of the CSF2, IL3, IL8, and PRF1 genes.

Table 2. Genes involved in the resistance (highlighted in red) and sensitivity (highlighted in green) to olaparib in androgen-dependent LNCaP prostate cancer cells.

KEY RESEARCH ACCOMPLISHMENTS:

- Successful synthesis and purification of 5F02 analogs with different chemical properties.
- The effect of histone-dependent PARP-1 inhibitors on androgen-dependent and -independent activation of AR signaling was evaluated.
- The functional antitumor activity of 5F02 and its analogs was examined in androgen-dependent and castration-resistant PC cells. 5F02 and its analogs demonstrated superior antitumor activity compared with NAD-like clinically relevant PARP-1 inhibitors olaparib, veliparib, and rucaparib.
- Physicochemical and ADME properties of 5F02 and its analogs were examined.

CONCLUSION: Contemporary therapeutic agents, such as abiraterone and enzalutamide, have shown impressive results in pre- and post-chemotherapy settings, prolonging the survival of patients with CRPC. However, nearly all patients ultimately develop resistance to anti-androgen therapeutics. Therapeutic failure of anti-androgen therapeutics is often accompanied by various molecular alterations resulting in androgen-independent activation of AR signaling pathway. PARP-1 supports AR transcriptional function. Therefore, PARP-1 inhibitors can be effective against both androgen-dependent and -independent activation of AR signaling. Our group was the first to identify agents that specifically target the histone-dependent route of PARP-1 activation, a mechanism that is unique to PARP-1. The proposal described herein strives to harness the therapeutic potential of our proprietary histone-dependent PARP-1inhibitors and apply our findings to the development of therapeutics for patients with castration-resistant prostate cancer. The proposed strategy not only carries promise as a stand-alone approach, but likely can also dovetail with existing pharmaceutical tactics for prostate cancer. If the idea presented here is proven viable, significant clinical rewards are expected.

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2. Makhov P, Sohn JA, Serebriiskii IG, FazliyevaR, Khazak V, Boumber Y, Uzzo RG, Kolenko VM. CRISPR/Cas9 genome-wide loss-of-function screening identifies druggable cellular factors involved in sunitinib resistance in renal cell carcinoma. British Journal of Cancer. 2020 Sep 24. Online ahead of print.

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

The faculty of the UND recognizes the value of periodic, scheduled reviews with graduate student and postdoctoral fellow trainees. As a university that prides itself on excellent science and mentoring, we believe that an authentic and documented discussion helps to re-enforce trainee strengths, and to identify and remedy any limitations or concerns. Such periodic reviews are further supported by the Postdoctoral Training Committee, chaired by its Director, Dr. Nechaev, who are available to provide support, training, and resources as needed to enable all trainees to be maximally competitive in the job market, and to improve or acquire specific skills identified in the medical school. In addition, programs available to all students during the year, including the popular the Science Writing course, the annual Postdoc and Grad Student Research Day, mandatory ethics training, and frequent career lecturers, help to complement the laboratory experience. We do not have a proscribed Individualized Development Plan, believing that this goal can be achieved by many approaches. However, we have mandated that all trainees, regardless of their funding source, have annual (at least) planning meetings with their Principal Investigator. We also support graduate students that we host on UND campus, who obtain their degrees from a number of area institutions. In these instances, we comply with their home institution's policies and forms. Regardless, all IDPs must include: documentation of career goals and what is required to achieve those goals; a list of trainee strengths, challenges and plans for the future to address those challenges; and an opportunity for the trainee to respond and provide feedback to their mentor. For any postdoctoral fellow to be appointed to our long-standing T32, or one of our other fellowships, the Principal Investigator must sign a statement confirming that annual (at least) IDPs will be conducted. Moreover, all T32 and Fellowship recipients receive a second IDP from Dr. Comb, which focuses on skill development and career design.

Our project provided substantial training opportunities for high school and undergraduate students in my lab. Training included the development of experimental design, troubleshooting, conducting experiments with cell cultures, generating transgenic Drosophilae, confocal microscopy, image analysis, as well as record keeping on experimental procedures, oral presentations at laboratory seminars, and poster preparation. The overwhelming majority of experiments described above were carried out by one high school student, Shri Patel, and three undergraduate students, Haily Datz, Cody Boyle, and Brett MacLeod, as well as graduate students Sayem Bhuiyan and Gbolahan Bamgbose. Our postdoctoral fellows were actively involved in training the students and providing oversight of their experimental work, as well as analysis of results and preparing them for publication.

Brett MacLeod and Cody Boyle, undergraduate students in the lab, have devoted 100% of their research time to this project. By participating in this project, Brett and Cody have now mastered all techniques used in the lab, and they are currently mentoring and training two incoming high school students and one undergraduate student. Recently, they single-handedly implemented the embryo fluorescent in situ hybridization method.

With the help of our technician, Sarah Johnson, Brett MacLeod and Cody Boyle have generated a polyclonal antibody against PARG phospho-peptides and carried out several key experiments characterizing the new antibodies, using Western blot analysis. Partly because of the experimental skills acquired while working in my lab, these students have been admitted to the Ph.D. program at UND, starting in August of 2020. Haily Datz has been accepted to UND Medical School. Michelle Ampofo, the former high school student in my lab, has been accepted in the undergraduate STEM program at Drexel College. Shri Patel, the high school student in my lab, was awarded second place at the 69th Annual North Dakota State Science and Engineering Fair.

How were the results disseminated to communities of interest?

Students working in my lab have reported their findings to their home group seminar series, in national and international conferences, and during the regional scientific fair meetings.

Our results will be reported as posters during one international meeting this summer and at the annual UND Epigenetics Symposium.

All recombinant plasmids, transgenic constructs, and mutant Drosophila stocks obtained in specific objectives 1 - 3 have been shared with other research teams: Lama Tarayrah (Weizmann Institute of Science, Rehovot, Israel); L Alberto Baena-Lopez (Sir William Dunn School of Pathology, Oxford, UK); Nicolas Buchon (Cornell University, Ithaca, NY); Jordan Kryza (UCLA, Los Angeles, CA); Ke Zhang (Johns Hopkins University, Baltimore, MD); Oyinkan (Onyx) Adesakin (University of Sussex, Brighton, UK); Vladimir Kolenko (Fox Chase Cancer Center); Dmitry Markov, Ph.D. (Rowan University, NJ).

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

During the next reporting period we plan to accomplish following tasks:

To Specific Aim1: 1) To determine the role of mutations in DNA damage-repair genes for sensitivity of PC cells to histone-dependent PARP-1 inhibitors. The proposed studies will address the causal role of the mutations in DNA-repair genes for sensitivity of PC cells to histone-dependent PARP-1 inhibitors. These studies will be performed using parental (PTEN-negative) and PTEN-expressing PC-3 cells. 2) To examine pharmacokinetic (PK) profile of histone-dependent PARP-1 inhibitors. The following parameters will be calculated: Cmax, Tmax, half-life, and area under the curve (AUC). These studies will be performed in collaboration with the Moulder Center for Drug Discovery Research. 120 male C.B17/Icr-scid mice will be used for these experiments. 3) Evaluate acute and chronic toxicity of histone-dependent PARP-1 inhibitors. Evaluate acute and chronic toxicity of histone-dependent PARP-1 inhibitors. A single escalating dose study will be used to examine acute toxicity in C.B17/Icr-scid mice. Chronic toxicity will be examined using a 3-week course of treatment. 160 male C.B17/Icr-scid mice will be used for these experiments.

To Specific Aim2: 1) To determine the effects of PARP-1 and PARG dysregulation during the onset of PC. We will knock down PARP-1 by expressing anti-PARP-1 shRNA in PC cells. Upon treatment with shRNA, we will monitor the expression of NF-kappa B-dependent genes. 2) To determine genomic sites of PARP-1 and pADPr occupancy in PC chromatin. We will determine genome-wide binding sites that PARP-1 occupies in chromatin and compare the distribution of these sites in normal prostate cells and PC-derived cells.

4. IMPACT:

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

Traditionally, research on cancer epigenetics has been focused on investigating either histone or DNA modifications. In contrast, this proposal targets PARP-1, a protein that simultaneously functions as an effector and as an epigenetic mark. We identify cancer-related genes targeted by PARP-1 through a genome-wide approach. Products of these genes can serve as biomarkers for PARP-1 inhibitor sensitivity in future clinical trials involving our new histone-dependent inhibitors. In addition, the antitumor activity of a novel class of histone-dependent PARP-1 inhibitors is tested in primary PC cells, as well as a xenograft animal model of human PC. Technologically, we have developed a method of identifying histone-dependent PARP-1 inhibitors using the histone-dependent route of PARP-1 activation. Thus, we bypass off-target effects of classical NAD-dependent PARP-1 inhibitors. Also, since the histone-dependent activation route is unique to PARP-1, our novel histone-dependent PARP-1 inhibitors afford greater specificity.

We explore the efficacy of novel PARP-1 inhibitors against castration-resistant PC cells, which are notoriously difficult to treat, as they are resistant to most conventional therapeutic regimens. Notably, conventional PARP-1 inhibitors act via an AR-dependent route of transcription activation (3); thus, they are only effective against AR-positive PC cells. As shown in our studies, our histone-dependent PARP-1 inhibitors, on the other hand, have a completely different molecular mechanism of action (see below) and effectively suppress growth of both AR-positive and AR-negative PC cells, both *in vitro* and *in vivo*.

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?
My laboratory is a part of the UND medical school. The university provides outstanding education opportunities for diverse students to engage in hands-on research in STEM disciplines. Research completed for this grant in my laboratory has been an integral part of undergraduate and graduate student training. All experimental systems developed for this project were used to train undergraduate students (100% effort on the project) and several high school students. Two of our students, who made major contributions to the project, will be continuing their education as a Ph.D. student at UND.

5. CHANGES/PROBLEMS:
Nothing to Report

6. PRODUCTS:
Publications in this period are listed below. Other manuscripts are in preparation.

1. Divan A, Sibi MP, Tulin A. 2020. Structurally unique PARP-1 inhibitors for the treatment of prostate cancer. Pharmacol Res Perspect. 8(2):e00586.

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7. Fox Chase Cancer Center website - https://www.foxchase.org/news/2020-08-31-fox-chase-researchers-find-novel-histone-dependent-parp-1-inhibitors-more-effective-at-treating-prostate-and-renal-cancers

FirstWord Pharma - https://www.firstwordpharma.com/node/1753563

8. FirstWord Pharma supplies global news and intelligence to the pharmaceutical industry. The service provides the top industry news stories on a daily basis in a format that is quick and easy to access so that users can always be in-the-know about the latest news and developments in their industry.

News Break - https://www.newsbreak.com/news/2051247257054/fox-chase-researchers-find-novel-histone-dependent-parp-1-inhibitors-more-effective-at-treating-prostate-and-renal-cancers

9. News Break is the Nation's #1 Intelligent Local News Platform. By forging close partnerships with thousands of local publishers and businesses around the country, News Break's priority is to help a new generation of readers find and engage with vital, locally published content and information.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS:

What individuals have worked on the project?

Alexei Tulin (PI)
Danping Gou (Scientific Associate)
Atreyi Ghartak (Scientific Associate)
Iaroslava Karpova (postdoctoral associate)
Haily Datz (undergraduate student) (UND, ND, USA)
Victor Gromoff (undergraduate student) (UND, ND, USA)
Breanna McLain (undergraduate student) (UND, ND, USA)
Cody Boyle (undergraduate student) (UND, ND, USA)
Brett MacLeod (undergraduate student) (UND, ND, USA)
Sayem Bhuiyan (graduate student) (UND, ND, USA)

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?

•Type of Partner Organization

Fox Chase Cancer Center, Philadelphia USA
Temple University, Philadelphia USA

•Name

Dr. Vladimir Kolenko, Ph.D.
Dr. John Gordon, Ph.D.

•Location

Fox Chase Cancer Center, Philadelphia USA
Temple University, Philadelphia USA

•Partner's contribution to the project

Collaborators

8. SPECIAL REPORTING REQUIREMENTS:

Nothing to Report

9. APPENDICES:

Nothing to Report