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TITLE: Direct Targeting of the FKBP52 Cochaperone for the Treatment of Castration-Resistant Prostate Cancer

PRINCIPAL INVESTIGATOR: Artem Cherkasov

CONTRACTING ORGANIZATION: University of British Vancouver
Canada

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Marc B. Cox, Artem Cherkasov, Jaideep Chaudhary

E-Mail: mbcox@utep.edu, acherkasov@prostatecentre.com, jchaudhary@cau.edu

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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

University of Texas at El Paso
500 W. University Ave.
El Paso, TX 79968-0587

University of British Columbia
Prostate Centre at VGH
2660 Oak St.
Vancouver, BC, Canada
V6H 3Z6

Clark Atlanta University
223 James P. Brawley Dr. SW
Atlanta, GA 30314-0000

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14. ABSTRACT

Prostate cancer affects one in seven men in the United States and is a major leading cause of cancer death among men. Current treatment strategies exploit the dependence of AR for hormone activation and current therapies are ineffective in castration resistant prostate cancer (CRPC). Based on this rationale, we are pursuing a unique non-AR based strategy. The folding, activation, and nuclear translocation of steroid hormone receptors involves no less than twelve proteins and at least four distinct complexes. At least one of these proteins, the FKBP52 cochaperone, is a highly promising therapeutic target for the disruption of a number of mechanisms important in prostate cancer. The proposed research is focused on the preclinical development of GMC1, a drug-like small molecule that targets FKBP52 regulation of steroid hormone receptor activity. During the first year of this award we have made progress in the hit-to-lead optimization process and have identified a number of novel derivatives with activity. We have also established protocols and assays for assessing lead drug effects in cellular and animal models.

15. SUBJECT TERMS

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A. INTRODUCTION

Prostate cancer affects one in seven men in the United States and is a major leading cause of cancer death among men. Current treatment strategies exploit the dependence of AR for hormone activation and current therapies are ineffective in castration resistant prostate cancer (CRPC). Based on this rationale, we are pursuing a unique non-AR based strategy. The folding, activation, and nuclear translocation of steroid hormone receptors involves no less than twelve proteins and at least four distinct complexes. At least one of these proteins, the FKBP52 cochaperone, is a highly promising therapeutic target for the disruption of a number of mechanisms important in prostate cancer. The proposed research is focused on the preclinical development of GMC1, a drug-like small molecule that targets FKBP52 regulation of steroid hormone receptor activity. The major goals of this research are to perform hit-to-lead optimization of GMC1 to improve drug solubility and potency, investigate the drug binding site and molecular mechanism of action in cellular models of prostate cancer, and conduct pre-clinical evaluation of our most promising lead compounds in animal models of prostate cancer.

B. KEYWORDS

Prostate cancer, castration-resistant prostate cancer, androgen receptor, glucocorticoid receptor, progesterone receptor, testosterone, FKBP52, FKBP4, FKBP51, FKBP5, immunophilin, cochaperone, beta-catenin, anti-androgen, pre-clinical, FKBP inhibitor

C. ACCOMPLISHMENTS

C.1 Major Goals of the Project as Outlined in the Approved SOW

The major goals for years 1-2 of the project are outlined below.

Specific Aim 1: Use structure-based drug design methodology and in silico library screening to identify small molecules targeting the FKBP52 PPIase pocket.

Major Task 1: Conduct large-scale in silico screen against the FKBP52 PPIase pocket

Specific Aim 2: Perform a detailed evaluation of all candidate drug compounds in multiple cellular models of prostate cancer.

Major Task 2: Functional screening of hit molecules and molecule modifications

Major Task 3: Verify drug-binding site for the most promising lead molecules.

Milestone 1: Seek patent protection for the 10 most promising lead molecules

Major Task 4: Characterize drug effects in cellular models of prostate cancer and characterize mechanism of action

Specific Aim 3: Perform preclinical evaluations in murine prostate cancer models.

Major Task 5: Assess in vitro efficacy of lead molecules

Milestone 2: Publication on novel drugs and their in vitro characterization

Major Task 6: Perform PK/PD on selected candidate compounds

C.2 Accomplishments Under These Goals

University of Texas at El Paso Site (Cox, PI):

In year 1, we began screening the novel GMC1 derivatives identified in the *in silico* hit-to-lead optimization being performed at the Vancouver Prostate Centre site (see below for more details) for anti-AR activity in order to identify new lead drug molecules with novel chemistry with which we can pursue composition of matter patents. In addition, we performed functional mutagenesis to verify the drug target site on FKBP52 by showing that mutations in the PPIase pocket (proposed GMC1 target site) that did not affect FKBP52 regulation of AR abrogated GMC1 inhibition. These data strongly suggest GMC1 targeting at this site. For year 2, we proposed to complete this screening process to identify new leads based on GMC1 in addition to identifying completely new chemotypes independent of GMC1 to pursue as possible drug candidates. In addition, we proposed to begin the process of patenting these new leads and characterizing them for effects in cellular and animal models of prostate cancer in year 2. It should be noted that the screening process was slower than planned due to a lack of medicinal chemistry support and purchasing derivatives to test proved to be overly expensive and slow. While this put us a little behind in our proposed timeline, we are now in a position to move forward with new leads and the approach will not change. We should be on track to complete most, if not all, of the proposed tasks and milestones by the end of year 3. As detailed below, we secured sponsored research agreements that provided the much-needed medicinal chemistry support and this significantly advanced the screening for, and identification of, leads. During this time Dr. Chaudhary's group continued with the mechanistic characterization of GMC1, the data from which will be relevant to any derivatives we pursue in the future. In addition, these mechanistic data are critical to publishing the initial manuscript on GMC1. The progress to-date is summarized below and we have made an effort to detail where we are behind in the timeline and when we plan to complete tasks.

Aim 2, Major Task 2: Functional screening of hit molecules and molecule modifications

Structure Activity Relationship (SAR) Screening for GMC1 Analogs: As mentioned above, we secured sponsored research agreements with Maia Biotech (https://maiabiotech.com/) early in year 2 in which Maia would provide the needed chemistry support, and, in return, Maia Biotech gets first rights to negotiating licensing of any novel leads that result. This not only directly complements the needs of this project but puts these technologies on a potential path for commercialization in the future. Based on knowledge of our previous SAR, we worked with the selected chemistry vendor, WuXi AppTec, to guide the synthesis of analogues of GMC1 with the goal of increasing efficacy, reducing toxicity, and ensuring bioavailability of the compound. Ease of preparation, potential amenability to parallel synthesis and the ability to generate diversity from late-stage intermediates was assessed. As detailed in **Figure 1**, this led to a modifications library consisting of 97 molecules that were screened first at a single high dose (25 uM) for inhibition of AR activity in MDAkb2 cell reporter assays. Any analogs that inhibited AR activity by 75% or more were then screened in full dose response curves to determine the IC50. From these data, we selected 5 GMC1 analogs that displayed significantly increased potency to send for ADME, which is also being performed through contract with WuXi Apptec (**Aim 3, Major Task 6**). Those ADME studies are currently ongoing and should be completed in the next month. It should also be noted that all 5 leads that were selected represent novel chemotypes that we can pursue composition of matter for; a major goal of this screening approach. Upon completion of ADME, the 2-3 leads with the best PK/PD profiles will be selected for patent protection and further characterization.

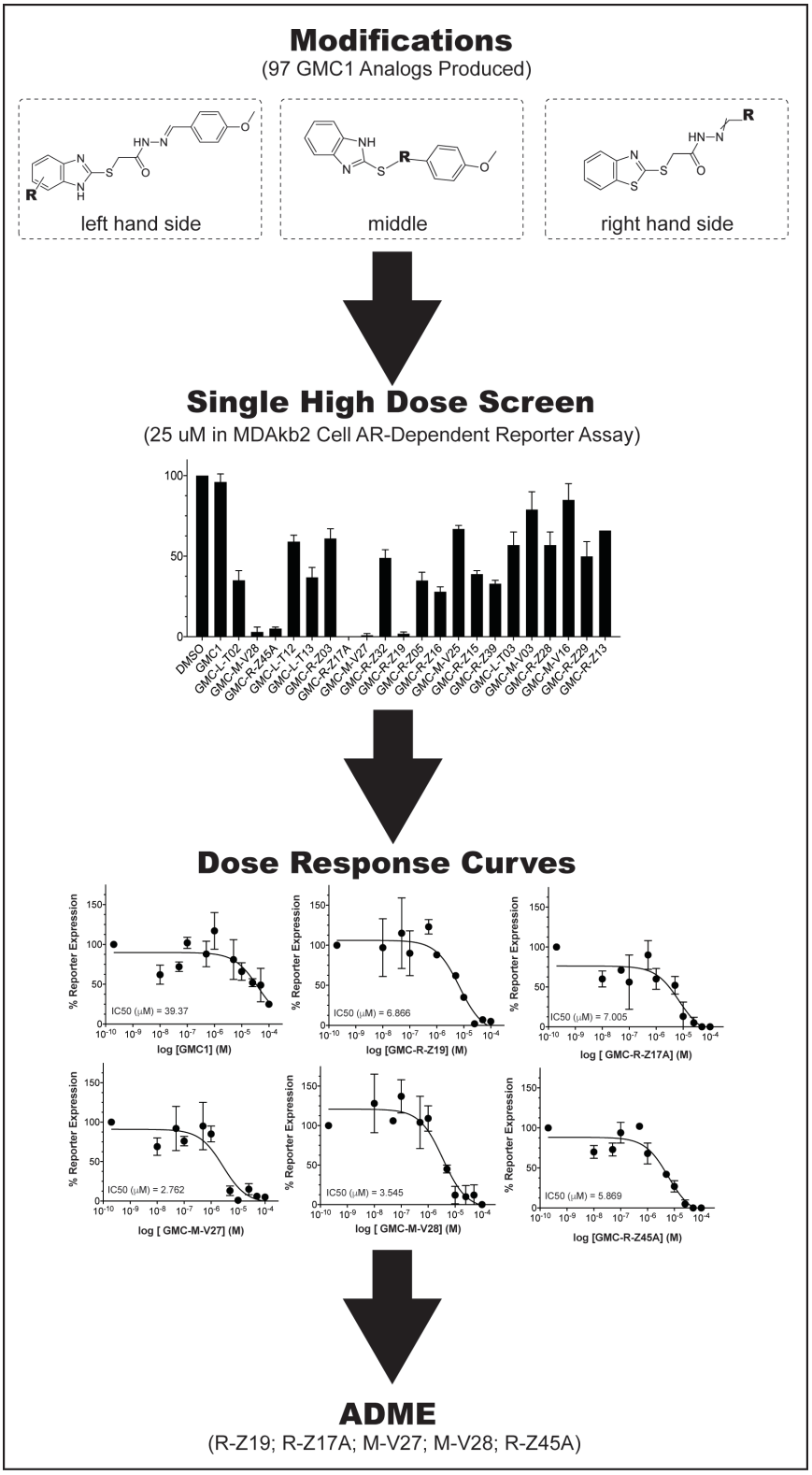

Figure 1: Structure-activity relationship (SAR) analysis of GMC1 derivatives. SAR aided in the synthesis of analogues of GMC1 with the goal of increasing efficacy, reducing toxicity and insuring bioavailability of the compounds, generating an initial modification library consisting of 97 molecules. Molecules were assessed for the ability to inhibit AR-mediated luciferase expression at a single high concentration (25μM) in MDA-kb2 cells. Molecules that showed inhibition at 25μM were assessed in full dose response curves to determine the IC50. MDA-kb2 cells were treated with 200 pM DHT with a range of derivative concentrations. Any molecule in the low μM range was then moved to the next step in screening ADME properties in order to ensure that derivatives contain suitable properties for formulation and oral dosing.

Structure-Based Screening for Novel FKBP52 Specific Inhibitors: As initially reported, our initial *in silico* screen that led to the identification of GMC1 was of limited scope and we proposed to continue our search for unique scaffolds by performing a broader *in silico* screen to generate a list of potential hits for functional screening. The Cherkosov group completed this broader *in silico* screen in year 2 as detailed below and that led to the identification of 107 potential hits for functional screening. As detailed in **Figure 2**, we first screened these molecules at a single high dose (25 uM) for inhibition of AR activity in MDAkb2 cell reporter assays. Any analogs that inhibited AR activity by 75% or more were then screened in full dose response curves to determine the IC50. From these data, we identified 3 hits that displayed inhibition of AR activity in the low micromolar range, with Z18027257 being the most potent with an IC50 of 2 uM. It should be noted that these 3 hits represent entirely new structures that can be pursued and patented independent of each other as well as independent of GMC1. We will fully characterize these hits over the next two months for FKBP52-specific AR inhibition and then pursue IP protection as they move forward in characterization and development process.

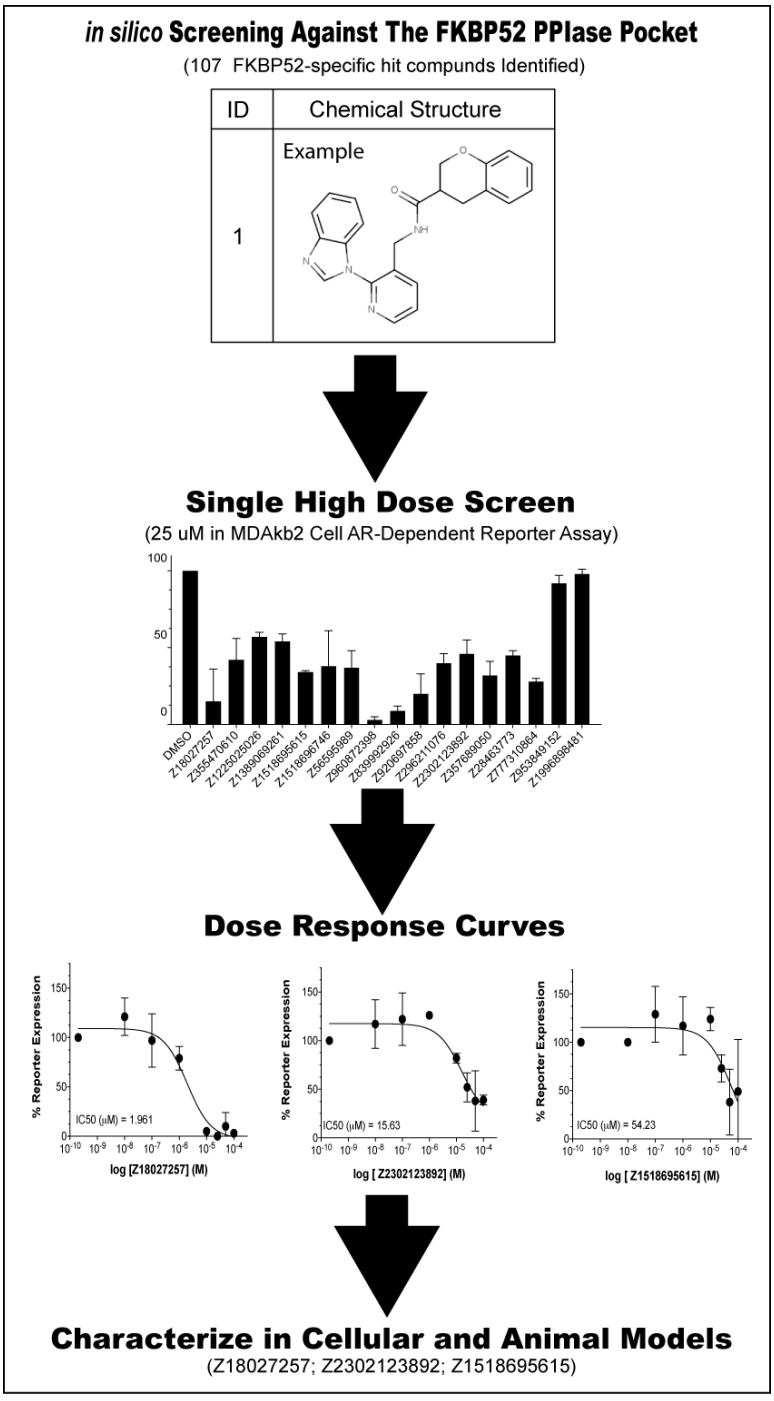

Figure 2: Identification of novel FKBP52-specific hit compounds. Structure-based drug design methodology and *in silico* library screening was used to identify 107 molecules targeting the FKBP52 PPIase pocket (see below for details on the *in silico* screen). Molecules were assessed for the ability to inhibit AR-mediated luciferase expression at a single high concentration (25 μM) in MDA-kb2 cells. Molecules that showed inhibition at 25 μM were assessed in full dose response curves to determine the IC50. MDA-kb2 cells were treated with 200pM DHT with a range of derivative concentrations. Molecules in the low μM range will be tested in AR-mediated luciferase assays to assess FKBP52 specificity in mouse embryonic fibroblast derived from FKBP52 knockout mice (52KO MEFs). A detailed evaluation of all candidate molecules will be tested in multiple cellular and animal models of prostate cancer.

Major Task 3: Verify drug-binding site for the most promising lead molecules

As detailed in the year 1 report and above, we previously demonstrated that mutations in the proposed GMC1 binding site, the FKBP52 PPIase pocket, abrogated the GMC1 inhibitory effect on AR activity. These data strongly suggest the PPIase pocket as the drug target site. We now have these mutations for use as a tool in assessing any new leads. However, it did not make sense to test every molecule for effects on these mutations. Thus, we have waited until new lead molecules could be identified. As detailed above we now have new leads identified both from the GMC1 SAR analysis as well as novel FKBP52-specific hits identified from the *in silico* screens. These new lead and hit molecules, no more 8 molecules in total, will be screened against these mutations as art of the characterization process discussed below in our plans for the next reporting period.

Milestones 1: Seek patent protection for the 10 most promising lead molecules; and **Milestone 2**: Publication on novel drugs and their *in vitro* characterization

As discussed above, the screening process was a bit slower than anticipated. However, as detailed in **Figures 1**, we now have identified a number of new lead molecules that represent unique chemotypes for which we can seek composition of matter protection. The ADME will be completed in the next month and we will seek protection for those molecules that show favorable PK/PD profiles; likely 2-3 molecules. In addition, we will seek IP protection for a small number of new FKBP52-specific hits that were identified from the in silico screens detailed in **Figure 2**. We anticipate provisional patents being submitted by December, 2019.

In addition to patent protection, now that we have data detailing the mechanism of GMC1 action on the AR signaling pathway (see data detailed below), we are now in a position to submit the initial manuscript detailing the identification, molecular and cellular characterization, and preclinical evaluation in animals of GMC1. We are currently in the process of preparing this manuscript and anticipate submitting by October, 2019. After provisional patents are submitted and the initial molecular, cellular and animal studies of the new leads are completed, we anticipate additional manuscripts being submitted by the end of year 3.

Vancouver Prostate Centre Site (Cherkasov, PI):

In the year 2 reporting period, we focused on identifying a lead molecule that will be characterized in both cellular and animal models of prostate cancer. On the basis of the binding pose of a simplified analog of FK506 co-crystalized with FKBP52 in crystal structure 4LAY, the Cherkasov group at VPC has performed a large-scale virtual screening of 132M compounds, and have completed the hit selection for wet lab evaluation.

Aim 1, Major Task 1: Conduct large-scale in silico screen against the FKBP52 PPIase pocket

Following our virtual screening pipe line (**Figure 3**) and *in silico* library screening to identify diverse small molecules targeting the FKBP52 PPIase pocket.

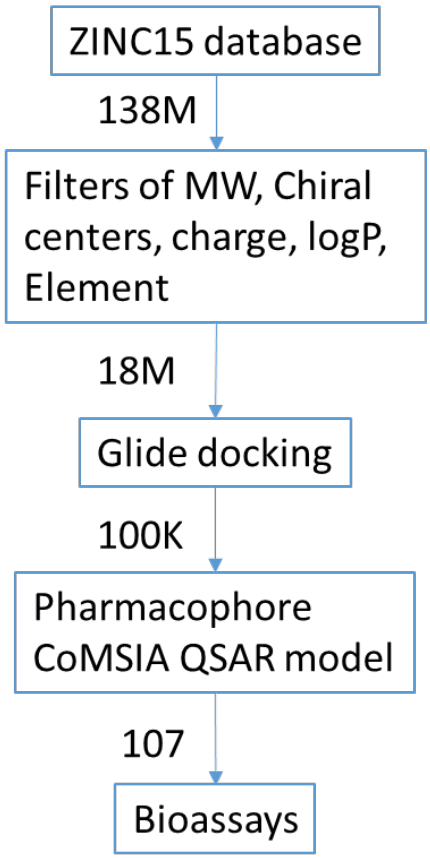

Figure 3. Virtual screening pipeline.

	Molecular Weight (up to, Daltons)							
LogP (up to)	350	375	400	425	450	500	>500	Totals, by LogP
0	7,851,555	1,659,590	153,838	3,109	1,997	1,771	1,081	9,671,860
1	8,282,385	4,533,805	687,115	16,735	10,918	9,887	2,844	13,540,845
2	11,838,100	19,430,906	2,223,959	70,389	50,966	46,616	9,781	33,660,936
2.5	12,743,184	9,272,525	1,912,892	79,998	62,770	58,890	12,118	24,130,259
3	12,758,220	8,713,599	2,441,222	119,485	96,881	100,479	22,938	24,229,886
3.5	9,523,725	11,164,695	1,786,726	152,873	130,166	145,168	41,443	22,903,353
4	209,148	2,628,141	227,769	1,213,359	154,184	184,604	84,452	4,617,205
Totals, by Weight	63,206,317	57,403,261	9,433,521	1,655,948	507,882	547,415	0	132,754,344 Protomers 1K Tranches

Figure 4. ZINC15 compound library downloaded for virtual screening.

More than 132M compounds of the ZINC15 library were download as shown in **Figure 4**. The downloaded compound library was subsequently filtered with OpenEye software. 18,000,000 compounds with (a) molecular weight between 350 and 500 Daltons, (b) 2 or 3 ring systems, (c) the number of chiral centers less than or equal to 2, (d) a charge of 0, (e) a logP between 2 and 5, and (f) elements H, C, N, O, F, P, S, Cl, Br and I were selected for Glide-SP docking evaluation. After docking, a pharmacophore model and a CoMSIA 3D-QSAR

model were constructed for ranking the Glide-docked compounds. Finally, after visual selection, 107 compounds were selected for biological evaluation. The Appendix tabulates these compounds.

Clark Atlanta University Site (Chaudhary, PI):

The lab is expected to receive new lead molecules based on GMC1 as well as new hits identified in the *in silico* screens detailed above after the ADME studies are completed and leads are selected. In the meantime, the Chaudhary group has continued to investigate the molecular mechanism of action and *in vitro* efficacy of GMC1, the lead compound to which all newly developed compounds will be compared. Hence it is extremely important that we establish the mechanism of action of GMC1 at the molecular level and define the level of *in vitro* efficacy in preparation for preclinical evaluation of new leads in murine models.

Aim 2, Major Task 4: Characterize drug effects in cellular models of prostate cancer and characterize mechanism of action; and **Aim 3, Major Task 5**: Assess in vitro efficacy of lead molecules

First, it is important to note that Dr. Chaudhary applied for IACUC approval for use of the Mercer University Vivarium (in collaboration with Ravi Palaniappan, Assoc. Prof. Mercer University). The IACUC protocol involved the use of GMC1 in nude/ SCIF mice through intravenous route. The protocol (A1904004) was approved (4/22/2019). The complete application package was then submitted to MRMC ACURO for approval (06/05/2019). The MRMC ACURO acknowledged the receipt of the proposal on 06/17/2019 and indicated that proposal is under review. Thus, the Chaudhary group is in a position to assess the *in vivo* effects of all new leads detailed above and can get started as soon as the molecules are received in the next month. In line with these goals, the following experiments were performed in year 2.

Experiment 1: Effect of GMC1 on proliferation of LNCaP and 22Rv1 cells (MTT assay).

The effect of GMC1 on proliferation was performed as stated in the proposal. The results demonstrated that GMC1 in the presence of the synthetic androgen R1881 significantly inhibited proliferation of LNCaP (**Figure 5A**) and 22Rv1 (**Figure 5B**) cells at 25um (**Figure 1**). Both LNCaP and 22Rv1 cells are androgen receptor positive and sensitive to androgen induced proliferation. In order to demonstrate that the effect of GMC1 is mediated in part by androgen receptor (AR), we performed a similar experiment with PC3 cells that lack AR. No change in the rate of proliferation in PC3 cells even in the presence of 100uM of GMC1 (**Figure 5C**) suggested that GMC1 action is mediated primarily through AR.

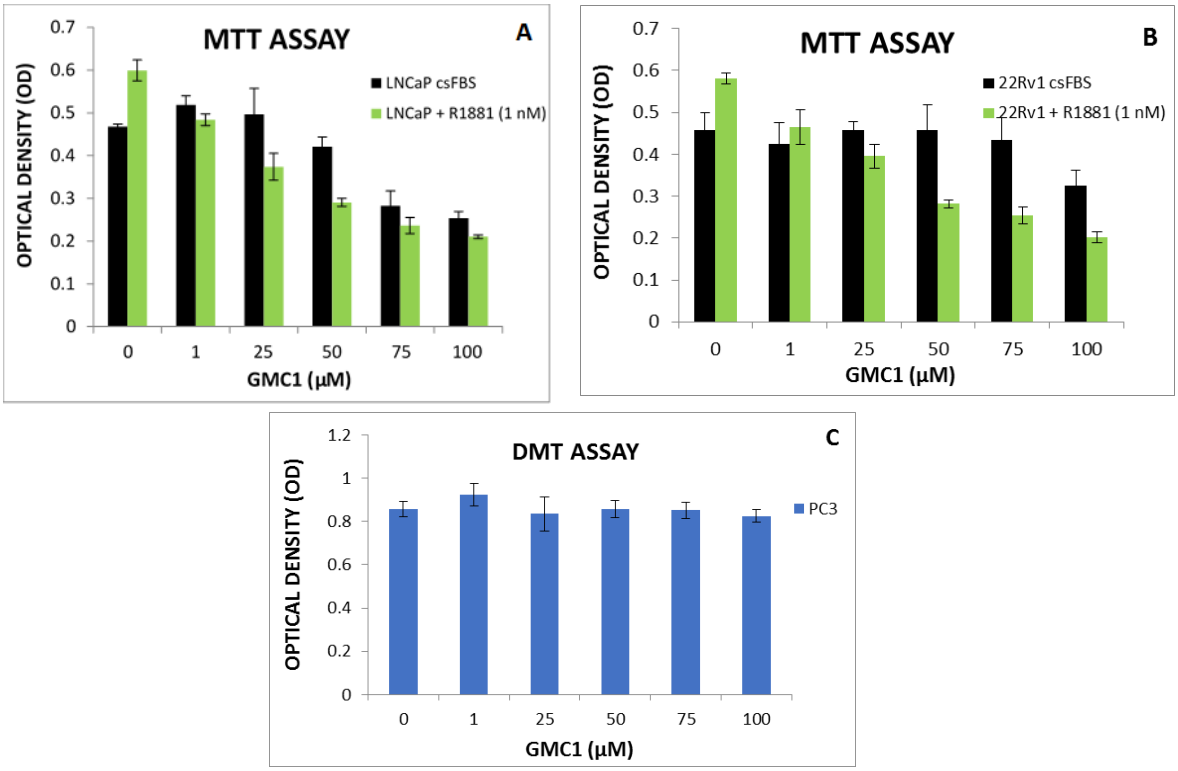

Figure 5: Effect of GMC1 on the proliferation. Proliferation of AR positive LNCaP (A) and 22Rv1 (B) cells and AR negative PC3 cells (C). The data is mean ±SEM of four different experiments in triplicate.

Experiment 2: Immuno-blot and Immuno-histo chemical analysis to confirm the effect of GMC1 on AR expression, cellular localization and interaction in both 22RV1 and LNCaP cells.

Based on the results in **Figure 5**, we anticipated that the effect of GMC1 on AR could be at multiple levels for example, GMC1 could alter a) the stability of AR (currently under investigation), b) expression of AR c) translocation of AR or d) alter the conformation of AR that modifies its associtaion with other AR chaperones required for optimal activity. Here we report that GMC1 alters the expression and nuclear translocation of AR in LNCaP (**Figure 6A**) and 22Rv1 (**Figure 6B**). Interestingly in both cell lines GMC1 also blocked translocation of FKBP52 to the nucleus.

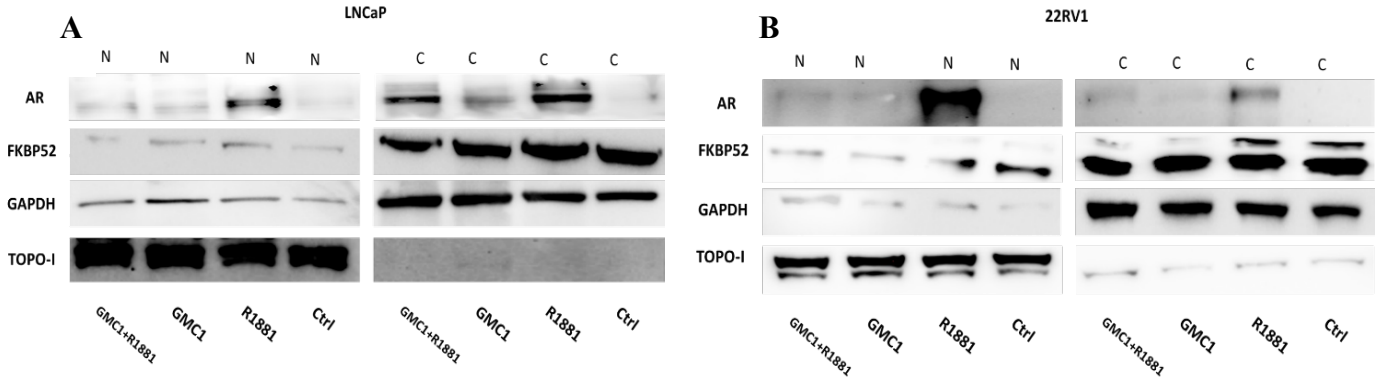

Figure 6: AR expression and cellular localization. Expression and localization in LNCaP (A) and 22Rv1 (B) cells after GMC1 treatment. Cytoplasmic and nuclear proteins were extracted from LNCaP (A) and 22RV1 (B) cells after GMC1, R1881, GMC1+R1881 or untreated vehicle only (Ctrl) treatments and analyzed by immunoblot analysis. The immunoblot analysis suggested that after treating LNCaP and 22RV1 with R1881, AR protein expression increased in the cytoplasm (C) and in the nucleus (N) indicating the AR has translocated to the nucleus. However, after treating LNCaP and 22RV1 cells with GMC1 (75µM), AR protein expression significantly reduced in both cytoplasm and nucleus even with R1881 treatment indicating that GMC1 not only affected AR translocation but expression also. TOPO-1 and GAPDH expression was used to confirm nuclear and cytoplasmic fractions and as loading control. The data is representative of 3 different experiments.

Immuno-cytochemistry was performed in order to further confirm the results shown in **Figure 6**. The effect of GMC1 on AR localization in LNCaP cells is shown in **Figure 7**. The results essentially support the observation reported in **Figure 6**. In brief, GMC1 treatment blocked the translocation of AR and FKBP52 to the nucleus. Observations suggest that in reposne to R1881 AR translocates to nucleus. However, in the presence of GMC1, AR remains associated with FKBPB2 (yellow color in Merged GMC1 treatment in cytoplasm) in the absence of R1881. Similar results were obtained in 22Rv1 cells (data not shown). Collectively, the results suggest that GMC1 blocks nuclear translocation of AR thus inhibiting its transcriptional activity.

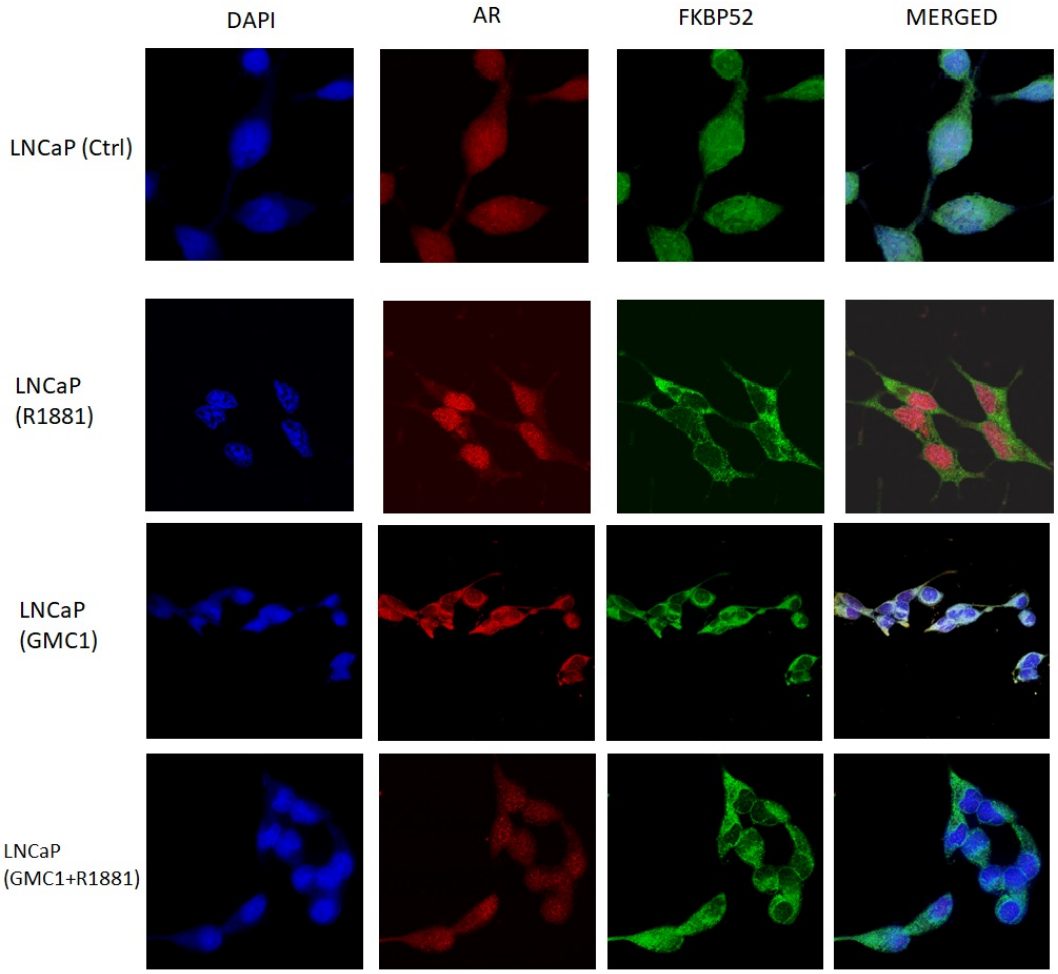

Figure 7: Confocal immune-fluorescence analysis to confirm that GMC1 alters AR signaling and nuclear translocation in LNCaP cells. ICC was performed to study the AR (Red) and FKBP52 (Green) interaction inside the cell before and after treating LNCaP cells with R1881 and GMC1. The merged panel is a merge between blue (DAPI, nucleus) AR and FKBP52. The data is representative of 3 experiments.

C.3 Opportunities for Training and Professional Development

Nothing to report

C.4 Results Disseminated to Communities of Interest

Nothing to report

C.5 Plans for Next Reporting Period

University of Texas at El Paso Site (Cox, PI):

Early in year 3 of the project the ADME studies will be completed and we will select a limited number of leads and hits from those detailed in **Figures 1 and 2** to move forward. We anticipate seeking provisional patent protection by December. In addition, we anticipate submitting our initial manuscript on GMC1 identification and characterization in October. During this time, the Cox group will work towards characterizing all new leads and hits for FKBP52-specific inhibition, for effects on chaperone and cochaperone association with AR, and for effects on endogenous AR-dependent gene expression. We will continue to work with Maia Biotechnology to move the new GMC1-based leads towards securing investigational new drug status in preparation for phase I trials in the future. It should be noted that, as part of the sponsored research agreement negotiations, we ensured that we as inventors retained the right to continue working on this line of research and that there would be no restrictions on publishing. Thus, this SRA will have no impact whatsoever on our ability to move these studies forward and disseminate the results. We will pursue the new hits detailed in **Figure 2** as a separate line of research and IP protection as they are independent of GMC1 and the sponsored research agreements with Maia Biotechnology.

Vancouver Prostate Centre Site (Cherkasov, PI):

In year 3, we will conduct the *in silico* hit-to-lead optimization of those new hits detailed in **Figure 2** after some initial molecular and cellular characterization is completed to select the top hit. In addition, the Vancouver prostate center will support additional PK/PD and formulation studies as needed on these new hit molecules.

Clark Atlanta University Site (Chaudhary, PI):

Now that new leads and hits have been identified (**Figures 1 and 2**), we will start the proposed animal studies to investigate the *in vivo* efficacy of these molecules in year 3. We have started the process to get MRMC ACURO approval and should be in a position to move forward with these studies early in year 3. Prior to animal studies we will develop toxicity profiles of the lead molecules *in vitro.* Finally, we will perform *in vitro* studies on lead compounds: MTT/ Annexin (PI), Matrigel transwell migration assay and anchorage-independent growth in a soft agar assay in a variety of androgen-sensitive and castration-resistant cell lines.

D. IMPACT

D.1 Impact on the Development of the Principle Discipline(s) of the Project

University of Texas at El Paso Site (Cox, PI): Nothing to report
Vancouver Prostate Centre Site (Cherkasov, PI): Nothing to report
Clark Atlanta University Site (Chaudhary, PI): Nothing to report

D.2 Impact on Other Disciplines

University of Texas at El Paso Site (Cox, PI): Nothing to report

Vancouver Prostate Centre Site (Cherkasov, PI): Nothing to report
Clark Atlanta University Site (Chaudhary, PI): Nothing to report

D.3 Impact on Technology Transfer

University of Texas at El Paso Site (Cox, PI):

As detailed above, the Cox group has secured a sponsored research agreement for GMC1 and derivatives that is aimed at supporting the medicinal chemistry and ADME needs of the project. As part of this agreement, Maia agreed to support the chemistry for SAR and ADME by contracting with WuXi AppTec, as well as supporting patent maintenance costs during this period. In return for this support, Maia gets rights to first negotiation for licensing of the leads that result. We also anticipate submitting additional composition of matter patents independent of this agreement for the novel FKBP52-specific hits that were identified in the *in silico* screens detailed above.

Vancouver Prostate Centre Site (Cherkasov, PI): Nothing to report
Clark Atlanta University Site (Chaudhary, PI): Nothing to report

D.4 Impact on Society Beyond Science and Technology

University of Texas at El Paso Site (Cox, PI): Nothing to report
Vancouver Prostate Centre Site (Cherkasov, PI): Nothing to report
Clark Atlanta University Site (Chaudhary, PI): Nothing to report

E. CHANGES/PROBLEMS

E.1 Changes in Approach and Reasons for Change

As detailed above, we got about 6 months behind in our timeline given that the screening process was slowed by the need to order molecules from a wide variety of obscure international vendors and the cost of procuring these molecules. This problem was solved by the sponsored research agreement with Maia Biotechnology and the medicinal chemistry support provided through this agreement. Thus, this delay does not change our approach.

University of Texas at El Paso Site (Cox, PI): Nothing to report
Vancouver Prostate Centre Site (Cherkasov, PI): Nothing to report
Clark Atlanta University Site (Chaudhary, PI): Nothing to report

E.2 Changes that Had a Significant Impact on Expenditures

University of Texas at El Paso Site (Cox, PI): Nothing to report
Vancouver Prostate Centre Site (Cherkasov, PI): Nothing to report
Clark Atlanta University Site (Chaudhary, PI): Nothing to report

E.3 Significant Changes in Use or Care of Human Subjects, Vertebrate Animals, Biohazards, and/or Select Agents

University of Texas at El Paso Site (Cox, PI): Nothing to report
Vancouver Prostate Centre Site (Cherkasov, PI): Nothing to report
Clark Atlanta University Site (Chaudhary, PI): Nothing to report

F. PRODUCTS

University of Texas at El Paso Site (Cox, PI):

The following book chapter references support from this award:

Mazaira, G.I., Zgajnar, N.R., Lotufo, C.M., Daneri-Becerra, C., ***Sivils, J.C., **Soto, O.B., **Cox, M.B.,** and Galigniana, M.D. (2019) Nuclear Receptors: A Historical Perspective. *Methods in Molecular Biology*. **1966**: 1-5.

Vancouver Prostate Centre Site (Cherkasov, PI): Nothing to Report
Clark Atlanta University Site (Chaudhary, PI): Nothing to report

G. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

G.1 Individuals Who Have Worked on the Project

University of Texas at El Paso Site (Cox, PI):

Name: Dr. Marc B. Cox
Project Role: PI
Researcher Identifier: https://orcid.org/0000-0001-7854-2676
Person months worked: 2.8
Contribution to Project: Dr. Cox provided oversight of the project, provided guidance and consultation to Ashley Payan, and assisted with the analysis and interpretation of data.

Funding Support: This project only

Name: Ashley Payan
Project Role: Graduate Student
Researcher Identifier: N/A
Person months worked: 12
Contribution to Project: Ashley conducted all experiments (reporter assays for screening derivatives), and collected and analyzed data.
Funding Support: This project only

Vancouver Prostate Centre Site (Cherkasov, PI):

Name: Dr. Artem Cherkasov
Project Role: PI
Researcher Identifier:
Person months worked: 2
Contribution to Project: Dr Cherkasov oversees all aspects of computational drug design, molecular modeling and bioinformatics, provides guidance and consultation to Dr. Kriti Singh, and assists with the analysis and interpretation of data.
Funding Support: Salary 100% covered by the University of British Columbia (no salary paid from this grant.

Name: Dr. Kriti Singh
Project Role: Post-doctoral Fellow
Researcher Identifier:
Person months worked: 12
Contribution to Project: Dr. Kriti conducted computational drug design, molecular modeling and bioinformatics

studies under the supervision of Dr. Cherkasov.
Funding Support: This project only

Name: Michael Llamosa
Project Role: Post-doctoral Fellow
Researcher Identifier:
Person months worked: 5
Contribution to Project: Dr. Llamosa worked alongside Dr. Kriti on computational drug design, molecular modeling and bioinformatics studies under the supervision of Dr. Cherkasov.
Funding Support: This project only

Name: Godwin Woo
Project Role: Master's Student
Researcher Identifier:
Person months worked: 9
Contribution to Project: Mr. Woo worked alongside Dr. Kriti on computational drug design, molecular modeling and bioinformatics studies under the supervision of Dr. Cherkasov.
Funding Support: This project only

Name: Eric LeBlanc
Project Role: Research Associate
Researcher Identifier:
Person months worked: 5
Contribution to Project: Dr. LeBlanc performed evaluation of compounds designed in Year 1, under the supervision of Dr. Cherkasov.
Funding Support: This project only

Name: Christophe Sanchez
Project Role: Co-Op
Researcher Identifier:
Person months worked: 2
Contribution to Project: Mr. Sanchez performed evaluation of compounds designed in Year 1, under the supervision of Dr. LeBlanc.
Funding Support: This project only

Clark Atlanta University Site (Chaudhary, PI):

Name: Dr. Jaideep Chaudharry
Project Role: PI
Researcher Identifier: https://orcid.org/0000-0002-4440-6585
Person months worked: 1
Contribution to Project: Dr. Chaudhary provided oversight of the project, provided guidance and consultation to Dr. Komaragiri, and assisted with the analysis and interpretation of data.
Funding Support: This project only

Name: Dr. Shravan Kumar Komaragiri
Project Role: Post-doctoral Fellow
Researcher Identifier: https://orcid.org/0000-0003-0889-9906
Person months worked: 12
Contribution to Project: Dr. Kumar established experimental protocols (cell culture, immune-histochemistry etc.), collected and analyzed data and managed the supply chain.

Funding Support: This project only

G.2 Changes in Active Other Support of the PD/PI(s) or Senior/Key Personnel Since the Last Reporting Period

University of Texas at El Paso Site (Cox, PI):

The following funding has been activated since negotiation and setup of this award:

Cox (PI) 6/1/2018-5/31/2019
Lizanell and Colbert Coldwell Foundation $70,000
A Novel Approach to Treating Castration Resistant Prostate Cancer
The overall goal of this project is to further our understanding of the mechanisms by which FKBP52 and beta-catenin regulate unique androgen-regulated, genome-wide transcriptional programs and define how targeting this mechanism affects those transcriptional programs.

1R13CA236020-01 Cox (PI) 11/1/2018-10/31/2019
NIH/NCI $5,000
This supported travel awards for trainees to attend the 2018 Annual Meeting of the Society for Basic Urologic Research (SBUR)

Cox (PI) 11/15/2018-11/14/2019
Maia Biotechnology Inc. $46,000
This Sponsored Research Agreement (SRA) with Maia Biotechnology supports the structure activity relationship analysis of our first-in-class FKBP52 targeting drug, GMC1, by providing medicinal chemistry support.

Cox (PI) 1/1/2019-12/31/2019
Maia Biotechnology Inc. $46,000
This Sponsored Research Agreement (SRA) with Maia Biotechnology supports the optimization of our AR BF3 targeting drug, MJC13, to improve potency and solubility, and to support studies aimed at securing IND status.

Cox (PI) 6/1/2019-5/31/2020
Lizanell and Colbert Coldwell Foundation $70,000
Proof-of-Concept Study of Surface-Directed AR Inhibitors for the Treatment of Prostate Cancer
This project supports the continued characterization of the mechanisms by which FKBP52 and beta-catenin regulate unique androgen-regulated, genome-wide transcriptional programs and defines how targeting these factors through targeting AR BF3 with MJC13 affects these unique transcriptional programs.

Vancouver Prostate Centre Site (Cherkasov, PI):

The following funding has been activated since negotiation and setup of this award:

Cherkasov (PI) 9/1/2018 – 8/31/2021
US Department of Defense USD $464,659
Design and evaluation of small molecules that target the dimerization interface of full-length and splice variant forms of the androgen receptor.
The overall goal of this project to evaluate that breaking or preventing human androgen receptor dimerization will bypass all drug-resistance mechanisms whereby antagonists such as enzalutamide are rendered ineffective by ligand binding domain (LBD mutants or when variants lacking the AR-LBD are expressed. Small drug inhibitors will be designed by computer assisted drug design (CADD) and evaluated via cell-based assays to inhibit full length and LBD-deleted androgen receptor mediated transcriptions of reporter molecules.

Cherkasov (PI) 4/1/2018-3/31/2021
Canadian Institutes of Health Research (CIHR) CAD $450,000
Design and evaluation of small molecules that target the dimerization interface of full-length and splice-variant forms of the androgen receptor as a potential treatment for advanced prostate cancer.
The goal of this project is to improve the potency and specificity of low molecular weight compounds to target the human androgen receptor dimerization interface using rational design.
We will employ biophysical approaches and cryogenic electron microscopy (cryo-EM) to investigate the molecular interaction between the AR and anti-dimer compounds.

Cherkasov (PI) 7/1/2018-30/6/2022
Canadian Foundation for Innovation CAD $9,000,000
Accelerated Drug Discovery Using Clinical Translation (ADDUCT).
ADDUCT expands upon existing CFI infrastructure grants to the VPC and to UBC's Advanced Structural Biology of Re-emerging Infectious Diseases (ASTRID) initiative, and also brings in expertise from the Centre of Drug Research and Development and the BC Cancer Agency, for targeted drug development to generate new drugs and treatment options for prostate, bladder and renal cancer patients. It will fund expansion in many areas of the bench-to-bedside pipeline, primarily focussed on targeted drug discovery and increasing the capacity for protein production, protein structural determination, and computer aided drug design.

Cherkasov (Co-PI) 4/1/2018-31/3/2021
Canadian Cancer Society CAD $1,000,000
Development of anti-estrogens with a novel mechanism of action for treatment of hormone resistant breast cancer.
From this study, we anticipate that our novel human estrogen receptor inhibitors will be further improved and will lead to new therapeutic strategies that can be used alternatively, complementarily, or synergistically with the current breast cancer treatments. The potential impact of the proposed research will be to create an entirely new class of drugs to treat breast cancer even in its most deadly, hormone-resistant forms. There is a great need for novel therapeutic strategies in breast cancer that can overcome tamoxifen resistance and improve patient survival.

Clark Atlanta University Site (Chaudhary, PI): Nothing to report

H. SPECIAL REPORTING REQUIREMENTS

This report is for a collaborative award (partnering PI option), and was prepared jointly by the three PIs. The tasks are clearly articulated for each responsible PI and project performance sites are clearly marked.

I. APPENDICES

None