Notice of Award

SPECIALIZED CENTER COOPERATIVE AGREEMENTS **Federal Award Date:** 04/21/2020

Department of Health and Human Services
National Institutes of Health

NATIONAL INSTITUTE ON MINORITY HEALTH AND HEALTH DISPARITIES

Grant Number: 2U54MD007595-11 REVISED
FAIN: U54MD007595

Principal Investigator(s):
Redacted by agreement
Guangdi Wang (contact), PHD

Project Title: Xavier RCMI Renewal Application-Overall

Dr. Meda, Dangale , PhD
Asst. VP-ORSP
1 Drexel Drive
New Orleans, LA 701251098

Award e-mailed to: ORSP@xula.edu

Period Of Performance:
Budget Period: 04/01/2019 – 12/31/2019
Project Period: 09/24/2009 – 12/31/2023

Dear Business Official:

The National Institutes of Health hereby revises this award (see "Award Calculation" in Section I and "Terms and Conditions" in Section III) to XAVIER UNIVERSITY OF LOUISIANA in support of the above referenced project. This award is pursuant to the authority of 42 USC 241 31 USC 6305 42 CFR 52 and is subject to the requirements of this statute and regulation and of other referenced, incorporated or attached terms and conditions.

Acceptance of this award including the "Terms and Conditions" is acknowledged by the grantee when funds are drawn down or otherwise obtained from the grant payment system.

Each publication, press release, or other document about research supported by an NIH award must include an acknowledgment of NIH award support and a disclaimer such as "Research reported in this publication was supported by the National Institute On Minority Health And Health Disparities of the National Institutes of Health under Award Number U54MD007595. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health." Prior to issuing a press release concerning the outcome of this research, please notify the NIH awarding IC in advance to allow for coordination.

Award recipients must promote objectivity in research by establishing standards that provide a reasonable expectation that the design, conduct and reporting of research funded under NIH awards will be free from bias resulting from an Investigator's Financial Conflict of Interest (FCOI), in accordance with the 2011 revised regulation at 42 CFR Part 50 Subpart F. The Institution shall submit all FCOI reports to the NIH through the eRA Commons FCOI Module. The regulation does not apply to Phase I Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) awards. Consult the NIH website http://grants.nih.gov/grants/policy/coi/ for a link to the regulation and additional important information.

If you have any questions about this award, please contact the individual(s) referenced in Section IV.

Sincerely yours,

Priscilla Grant
Grants Management Officer
NATIONAL INSTITUTE ON MINORITY HEALTH AND HEALTH DISPARITIES

Additional information follows

SECTION I – AWARD DATA – 2U54MD007595-11 REVISED

Award Calculation (U.S. Dollars)

Salaries and Wages	$1,212,779
Fringe Benefits	$265,570
Personnel Costs (Subtotal)	$1,478,349
Consultant Services	$109,500
Materials & Supplies	$195,366
Travel	$68,000
Alterations and Renovations	$500,000
Other	$424,000
Subawards/Consortium/Contractual Costs	$49,974
Publication Costs	$24,526
Equipment or Facility Rental/User Fees	$16,500
Federal Direct Costs	$2,866,215
Federal F&A Costs	$930,821
Approved Budget	$3,797,036
Total Amount of Federal Funds Obligated (Federal Share)	$3,797,036
Less Unobligated Balance	$125,000
TOTAL FEDERAL AWARD AMOUNT	$3,672,036
AMOUNT OF THIS ACTION (FEDERAL SHARE)	$0

SUMMARY TOTALS FOR ALL YEARS		
YR	**THIS AWARD**	**CUMULATIVE TOTALS**
11	$3,672,036	$3,672,036
12	$3,076,195	$3,076,195
13	$3,030,676	$3,030,676
14	$2,970,081	$2,970,081
15	$2,841,178	$2,841,178

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

Fiscal Information:

CFDA Name: Minority Health and Health Disparities Research
CFDA Number: 93.307
EIN: 1720635884A1
Document Number: UMD007595C
PMS Account Type: P (Subaccount)
Fiscal Year: 2019

IC	CAN	2019	2020	2021	2022	2023
MD	8039333	$3,672,036	$3,076,195	$3,030,676	$2,970,081	$2,841,178

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

NIH Administrative Data:
PCC: 17006 / **OC**: 41027 / **Released**: eRA Commons User Name 04/21/2020
Award Processed: 04/21/2020 07:01:38 PM

SECTION II – PAYMENT/HOTLINE INFORMATION – 2U54MD007595-11 REVISED

For payment and HHS Office of Inspector General Hotline information, see the NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm

SECTION III – TERMS AND CONDITIONS – 2U54MD007595-11 REVISED

This award is based on the application submitted to, and as approved by, NIH on the above-titled project and is subject to the terms and conditions incorporated either directly or by reference in the following:

a. The grant program legislation and program regulation cited in this Notice of Award.
b. Conditions on activities and expenditure of funds in other statutory requirements, such as those included in appropriations acts.
c. 45 CFR Part 75.
d. National Policy Requirements and all other requirements described in the NIH Grants Policy Statement, including addenda in effect as of the beginning date of the budget period.
e. Federal Award Performance Goals: As required by the periodic report in the RPPR or in the final progress report when applicable.
f. This award notice, INCLUDING THE TERMS AND CONDITIONS CITED BELOW.

(See NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm for certain references cited above.)

Research and Development (R&D): All awards issued by the National Institutes of Health (NIH) meet the definition of "Research and Development" at 45 CFR Part§ 75.2**.** As such, auditees should identify NIH awards as part of the R&D cluster on the Schedule of Expenditures of Federal Awards (SEFA). The auditor should test NIH awards for compliance as instructed in Part V, Clusters of Programs. NIH recognizes that some awards may have another classification for purposes of indirect costs. The auditor is not required to report the disconnect (i.e., the award is classified as R&D for Federal Audit Requirement purposes but non-research for indirect cost rate purposes), unless the auditee is charging indirect costs at a rate other than the rate(s) specified in the award document(s).

An unobligated balance may be carried over into the next budget period without Grants Management Officer prior approval.

This award is subject to the requirements of 2 CFR Part 25 for institutions to receive a Dun & Bradstreet Universal Numbering System (DUNS) number and maintain an active registration in the System for Award Management (SAM). Should a consortium/subaward be issued under this award, a DUNS requirement must be included. See http://grants.nih.gov/grants/policy/awardconditions.htm for the full NIH award term implementing this requirement and other additional information.

This award has been assigned the Federal Award Identification Number (FAIN) U54MD007595. Recipients must document the assigned FAIN on each consortium/subaward issued under this award.

This award is not subject to the Transparency Act subaward and executive compensation reporting requirement of 2 CFR Part 170.

In accordance with P.L. 110-161, compliance with the NIH Public Access Policy is now mandatory. For more information, see NOT-OD-08-033 and the Public Access website: http://publicaccess.nih.gov/.

This award provides support for one or more clinical trials. By law (Title VIII, Section 801 of Public Law 110-85), the "responsible party" must register "applicable clinical trials" on the ClinicalTrials.gov Protocol Registration System Information Website. NIH encourages registration of all trials whether required under the law or not. For more information, see http://grants.nih.gov/ClinicalTrials_fdaaa/

In accordance with the regulatory requirements provided at 45 CFR 75.113 and Appendix XII to 45 CFR Part 75, recipients that have currently active Federal grants, cooperative agreements, and procurement contracts with cumulative total value greater than $10,000,000 must report and maintain information in the System for Award Management (SAM) about civil, criminal, and administrative proceedings in connection with the award or performance of a Federal award that

reached final disposition within the most recent five-year period. The recipient must also make semiannual disclosures regarding such proceedings. Proceedings information will be made publicly available in the designated integrity and performance system (currently the Federal Awardee Performance and Integrity Information System (FAPIIS)). Full reporting requirements and procedures are found in Appendix XII to 45 CFR Part 75. This term does not apply to NIH fellowships.

Treatment of Program Income:
Additional Costs

SECTION IV – MD Special Terms and Conditions – 2U54MD007595-11 REVISED

Clinical Trial Indicator: Yes
This award supports one or more NIH-defined Clinical Trials. See the NIH Grants Policy Statement Section 1.2 for NIH definition of Clinical Trial.

INFORMATION: This revised award indicates that an unobligated balance may be carried over into the next budget period without Grants Management Officer prior approval.

THE FOLLOWING TERMS FROM THE PREVIOUS NOTICE OF AWARD LETTER ISSUED ON 6/20/2019 ALSO APPLY TO THIS AWARD:

INFORMATION: This award authorizes a carryover of $125,000 of the unexpended funds from the -09 year to the -11 year. The carryover is subject to the availability of funds. If the actual balance from the -09 year is less than anticipated, authorization for the -11 year is reduced accordingly.

THE FOLLOWING TERMS FROM THE PREVIOUS NOTICE OF GRANT AWARD ISSUED ON 03/07/2019 ALSO APPLY TO THIS AWARD:

RESTRICTION: This award is issued without a currently valid certification of IRB approval for the intervention phase of Project 1 with the following special condition: Only activities that are clearly severable and independent from intervention phase activities that involve human subjects may be conducted under this award until the project has received IRB approval consistent with 45 CFR Part 46 and certification of IRB approval has been submitted to and accepted by the NIMHD.

No funds may be drawn down from the payment system and no obligations may be made against Federal funds for intervention phase research involving human subjects at any site engaged in such research for any period not covered by both (1) the awardee's OHRP-approved Assurance and if performance sites are involved, each performance site's OHRP-approved Assurance(s) and (2) appropriate IRB approvals consistent with all OHRP-approved Assurances.

Failure to comply with this special condition can result in the suspension and/or termination of this award, withholding of support, audit disallowances, and/or other appropriate action.

REQUIREMENT: This award is issued as a cooperative agreement, a financial assistance mechanism in which substantial NIH scientific and/or programmatic involvement is anticipated in the performance of the activity. This award is subject to the Terms and Conditions of Award as set forth in the SPECIAL REQUIREMENTS section of RFA-MD-17-006, Research Centers in Minority Institutions (RCMI) (U54), NIH Guide to Grants and Contracts, 08/25/2017, which are hereby incorporated by reference as special terms and conditions of this award.

Copies of this RFA may be accessed at the following internet address:
http://www.nih.gov/grants/guide/index.html

Copies may also be obtained from the Grants Management Contact indicated in the terms of award.

These special Terms and Conditions of Award are in addition to and not in lieu of otherwise applicable OMB administrative guidelines, Federal Regulations, including HHS Grant Administration Regulations at 42 CFR Part 52, 45 CFR Part 75, and other HHS, PHS, and NIH Grant Administration policy statements.

The following administrative terms also apply:

REQUIREMENT: Use of humans and animals in any new activities must be requested prior to the start of the activity and must be approved in writing in advance by the NIMHD. See NOT-MD-08-002, "Guidance and Clarification on NCMHD Policy on Prior Approval for Subprojects and Pilot Projects Involving Human Subjects or Vertebrate Animals," NIH Guide to Grants and Contracts, April 29, 2008, which is hereby incorporated by reference as special terms and conditions of this award. See also NOT-OD-15-129, "Prior NIH Approval of Human Subjects Research in Active Awards Initially Submitted without Definitive Plans for Human Subjects Involvement (Delayed Onset Awards): Updated Notice," and NIH-OD-15-128, "Guidance on Changes That Involve Human Subjects in Active Awards and That Will Require Prior NIH Approval: Updated Notice."

Copies of these Notices may be accessed at the following internet address: http://www.nih.gov/grants/guide/index.html

Copies may also be obtained from the Grants Management Contact indicated in the terms of award.

REQUIREMENT: The awardee is required to follow the Data Sharing Plan included in the competing application and may not implement any changes in the plan without the written prior approval of the National Institute on Minority Health and Health Disparities.

REQUIREMENT: The recipient is required to follow the data and safety monitoring plan included in the application and may not implement any changes in the plan without the written prior approval of the NIMHD.

RESTRICTION: The clinical trial(s) supported by this award is subject to the plan dated December 15th, 2017 submitted to NIH and the NIH policy on *Dissemination of NIH-Funded Clinical Trial Information.* The plan states that the clinical trial(s) funded by this award will be registered in ClinicalTrials.gov not later than 21 calendar days after enrollment of the first participant and primary summary results reported in ClinicalTrials.gov, not later than one year after the completion date. The reporting of summary results is required by this term of award even if the primary completion date occurs after the period of performance.

RESTRICTION: This award is subject to additional certification requirements with each submission of the Annual, Interim, and Final Research Performance Progress Report (RPPR). The recipient must agree to the following annual certification when submitting each RPPR. By submitting the RPPR, the AOR signifies compliance, as follows:

> In submitting this RPPR, the SO (or PD/PI with delegated authority), certifies to the best of his/her knowledge that, for all clinical trials funded under this NIH award, the recipient and all investigators conducting NIH-funded clinical trials are in compliance with the recipient's plan addressing compliance with the NIH Policy on Dissemination of NIH-Funded Clinical Trial Information. Any clinical trial funded in whole or in part under this award has been registered in ClinicalTrials.gov or will be registered not later than 21 calendar days after enrollment of the first participant. Summary results have been submitted to ClinicalTrials.gov or will be submitted not later than one year after the completion date, even if the completion date occurs after the period of performance.

RESTRICTION: Stipends and payments made for educational assistance (e.g., scholarships, fellowships, and student aid costs) may not be paid from NIH research grant funds even when they would appear to benefit the research project (NIH GPS Section 7.9.1). Compensation must be in accordance with organizational policies consistently applied to both federally and non-

federally supported activities and must be supported by acceptable accounting records that reflect the employer-employee relationship. Under these conditions, the funds provided as compensation for services rendered are not considered stipend supplementation; they are allowable charges to Federal grants, including PHS research grants. (A stipend is a payment made to an individual under a fellowship or training grant in accordance with pre-established levels to provide for the individual's living expenses during the period of training. A stipend is not considered compensation for the services expected of an employee.) See the NIH Grants Policy Statement for allowable forms of student compensation, available at http://grants.nih.gov/grants/policy/nihgps/nihgps.pdf.

INFORMATION: Staff contacts and responsibilities.

STAFF CONTACTS
The Grants Management Specialist is responsible for the negotiation, award and administration of this project and for interpretation of Grants Administration policies and provisions. The Project Scientist will serve as the subject matter expert for the project and will be involved as described in the above-referenced FOA, including facilitating the coordination and collaboration on specific aims, goals, and Coordinating/Steering Committee meeting agendas; participating in the Coordinating/Steering Committee meetings; and assisting in the dissemination of research results including publications and scientific presentations as appropriate and in accordance with NIH and NIMHD publication policies. The Program Official will be responsible for the normal program stewardship, including scientific, programmatic and technical aspects of this project. The Program Official will attend and participate in the Coordinating/Steering Committee meetings with the Project Scientist. The Grants Management Specialist and Program Official will work together in overall project administration. Prior approval requests (signed by an Authorized Organizational Representative) should be submitted in writing to pg38h@nih.gov with a copy to the Grants Management Specialist. Requests may be made via e-mail.

Grants Management Specialist: Sy L. Shackleford at (301) 451-8542
Project Scientist: Dr. Benyam Hailu at (301) 594-8696
Program Official: Dr. Rina Das at (301) 496-3996

INFORMATION: This award reflects NIMHD approval of the proposed revised aims for Project #1 submitted by the grantee on February 19th, 2019. Significant additional changes in the aims, objectives or purposes of this project require NIMHD prior approval.

INFORMATION: In order to redistribute awards more evenly throughout the year, budget periods are being adjusted. This award is issued with a 9-month budget period and with 12 months of support. Continuation awards will cycle each year on January 1st.

INFORMATION: Although the budget period start date for this award is April 1st, this award includes funds for 12 months of support. Future year budget periods will cycle on December 1st. Allowable preaward costs may be charged to this award, in accordance with the conditions outlined in the NIH Grants Policy Statement, and with institutional requirements for prior approval. The NIH GPS can be found on the internet at http://grants.nih.gov/grants/policy/nihgps/nihgps.pdf.

INFORMATION: This award reflects the NIMHD's acceptance of the certification that all key personnel have completed education on the protection of human subjects, in accordance with NIH policy, "Required Education in the Protection of Human Research Participants," as announced in the June 5, 2000 NIH Guide (revised August 25, 2000) (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html).

Any individual involved in the design and conduct of the study that is not included in the certification must satisfy this requirement prior to participating in the project. Failure to comply can result in the suspension and/or termination of this award, withholding of support of the continuation award, audit disallowances, and/or other appropriate action.

INFORMATION: See "Federalwide Assurance Requirements" and "Certification of IRB Approval" under the Human Subjects Protections section in the NIH Grants Policy Statement (NIHGPS), for specific requirements and recipient responsibilities related to the protection of human subjects, which are applicable to and are a term and condition of this award. The NIHGPS can found on the internet at http://grants.nih.gov/grants/policy/nihgps/nihgps.pdf.

INFORMATION: None of the funds in this award shall be used to pay the salary of an individual at a rate in excess of the current salary cap. See the new Salary Limitations on Grants: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-181.html

INFORMATION: Unobligated balances may be used by the NIMHD to reduce or offset funding for a subsequent budget period.

INFORMATION: Regarding changes in scope, attention is called to the NIH Grants Policy Statement. The Change in Scope section is found in Section 8.1.2 at http://grants.nih.gov/grants/policy/nihgps/nihgps.pdf. The recipient must obtain prior approval from the NIMHD for a change in the direction, aims, objectives, purposes, or type of research or training, or other areas that constitute a significant change in the approved project. Specific examples are provided.

INFORMATION: Regarding allowability of selected items of cost, attention is called to the NIH Grants Policy Statement. The Selected Items of Cost section is found in Section 7.9.1 at http://grants.nih.gov/grants/policy/nihgps/nihgps.pdf.

INFORMATION: Honoraria are unallowable when the primary intent is to confer distinction on, or to symbolize respect, esteem, or admiration for, the recipient of the honorarium. A payment for services rendered, such as a speaker's fee under a conference grant, is allowable. See Section 7.9.1 at http://grants.nih.gov/grants/policy/nihgps/nihgps.pdf.

INFORMATION: This award includes funds awarded for consortium activity. Consortia are to be established and administered as described in the NIH Grants Policy Statement (NIH GPS). The referenced section of the NIH GPS is available at: http://grants.nih.gov/grants/policy/nihgps/nihgps.pdf. See "Consortium Agreements" in Section 15 for specific responsibilities and requirements for recipients and consortium participants, which are applicable to and are a term and condition of this award.

INFORMATION: For administrative and management concerns, contact the Grants Management Specialist, Sy L. Shackleford, at (301) 451-8542. For programmatic and scientific concerns, contact the Program Director, Dr. Rina Das at (301) 496-3996.

STAFF CONTACTS

The Grants Management Specialist is responsible for the negotiation, award and administration of this project and for interpretation of Grants Administration policies and provisions. The Program Official is responsible for the scientific, programmatic and technical aspects of this project. These individuals work together in overall project administration. Prior approval requests (signed by an Authorized Organizational Representative) should be submitted in writing to the Grants Management Specialist. Requests may be made via e-mail.

Grants Management Specialist: Sy Shackleford
Email: shacklefords@mail.nih.gov **Phone**: 301-402-1366

Program Official: Rina Das
Email: dasr2@mail.nih.gov **Phone**: 301-402-1366

SPREADSHEET SUMMARY

GRANT NUMBER: 2U54MD007595-11 REVISED

INSTITUTION: XAVIER UNIVERSITY OF LOUISIANA

Budget	Year 11	Year 12	Year 13	Year 14	Year 15
Salaries and Wages	$1,212,779	$1,212,779	$1,212,779	$1,212,779	$1,212,779
Fringe Benefits	$265,570	$265,570	$265,570	$265,570	$265,570
Personnel Costs (Subtotal)	$1,478,349	$1,478,349	$1,478,349	$1,478,349	$1,478,349
Consultant Services	$109,500	$130,500	$184,500	$67,500	$66,500
Materials & Supplies	$195,366	$169,466	$109,437	$95,252	$86,182
Travel	$68,000	$59,000	$51,250	$50,250	$49,000
Alterations and Renovations	$500,000				
Other	$424,000	$268,655	$252,557	$242,518	$240,211
Subawards/Consortium/Contractual Costs	$49,974	$50,181	$50,222	$50,222	$50,222
Publication Costs	$24,526	$23,526	$21,318	$18,870	$16,720
ADP/Computer Services				$102,000	$27,000
Equipment or Facility Rental/User Fees	$16,500	$1,500	$1,500	$1,500	$1,500
TOTAL FEDERAL DC	$2,866,215	$2,181,177	$2,149,133	$2,106,461	$2,015,684
TOTAL FEDERAL F&A	$930,821	$895,018	$881,543	$863,620	$825,494
TOTAL COST	$3,672,036	$3,076,195	$3,030,676	$2,970,081	$2,841,178

Facilities and Administrative Costs	Year 11	Year 12	Year 13	Year 14	Year 15
F&A Cost Rate 1	42%	42%	42%	42%	42%
F&A Cost Base 1	$2,216,241	$2,130,996	$2,098,911	$2,056,239	$1,965,462
F&A Costs 1	$930,821	$895,018	$881,543	$863,620	$825,494

PI: **Wang, Guangdi**	Title: Xavier RCMI Renewal Application-Overall	
Received: 12/15/2017	FOA: MD17-006	Council: 05/2018
Competition ID: FORMS-D	FOA Title: Research Centers in Minority Institutions (RCMI) (U54)	
2 U54 MD007595-11	Dual: AI	Accession Number: 4120621
IPF: 9416401	Organization: XAVIER UNIVERSITY OF LOUISIANA	
Former Number:	Department: Chemistry	
IRG/SRG: ZMD1 DRI (M1)	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) Year 11: 2,730,437 Year 12: 2,226,078 Year 13: 2,232,101 Year 14: 2,231,404 Year 15: 2,189,103	Animals: Y Humans: Y Clinical Trial: Y Current HS Code Evaluative Info HESC: N Special Topics: COVID-affected	New Investigator: Early Stage Investigator:
Senior/Key Personnel:	*Organization:*	*Role Category:*
Guangdi Wang PhD	Xavier University of Lousiana	PD/PI
Redacted by agreement	Xavier University of Lousiana	MPI

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE | **State Application Identifier**

1. TYPE OF SUBMISSION*

❍ Pre-application ❍ Application ● Changed/Corrected Application

4.a. Federal Identifier
MD007595

b. Agency Routing Number

2. DATE SUBMITTED
2017-12-15

Application Identifier

c. Previous Grants.gov Tracking Number
GRANT12536298

5. APPLICANT INFORMATION **Organizational DUNS*:** 020857876

Legal Name*: Xavier University of Lousiana
Department:
Division:
Street1*: 1 Drexel Drive
Street2:
City*: New Orleans
County: Orleans
State*: LA: Louisiana
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 70125-1098

Person to be contacted on matters involving this application
Prefix: Dr. First Name*: Dangale Middle Name: Last Name*: Meda Suffix: PhD
Position/Title: Asst. VP-ORSP
Street1*: 1 Drexel Drive
Street2:
City*: New Orleans
County:
State*: LA: Louisiana
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 70125-1098
Phone Number*: 504.520.5600 Fax Number: 504.520.7901 Email: dmeda@xula.edu

6. EMPLOYER IDENTIFICATION NUMBER *(EIN) or (TIN)** 720635884

7. TYPE OF APPLICANT* T: Historically Black Colleges and Universities (HBCUs)

Other (Specify):
Small Business Organization Type ❍ Women Owned ❍ Socially and Economically Disadvantaged

8. TYPE OF APPLICATION*
❍ New ❍ Resubmission
● Renewal ❍ Continuation ❍ Revision

If Revision, mark appropriate box(es).
❍ A. Increase Award ❍ B. Decrease Award ❍ C. Increase Duration
❍ D. Decrease Duration ❍ E. Other *(specify)* :

Is this application being submitted to other agencies?* ❍Yes ●No What other Agencies?

9. NAME OF FEDERAL AGENCY*
National Institutes of Health

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER
TITLE:

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*
Xavier RCMI Renewal Application-Overall

12. PROPOSED PROJECT
Start Date* Ending Date*
09/15/2018 09/14/2023

13. CONGRESSIONAL DISTRICTS OF APPLICANT
LA-002

SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: Dr. First Name*: Guangdi Middle Name: Last Name*: Wang Suffix: PhD
Position/Title: Professor
Organization Name*: Xavier University of Lousiana
Department: Chemistry
Division: Div. of Math. & Phys.Sciences
Street1*: 1 Drexel Drive
Street2:
City*: New Orleans
County:
State*: LA: Louisiana
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 70125-1098
Phone Number*: 5045205076 Fax Number: 5045207942 Email*: gwang@xula.edu

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested*	$11,650,521.00
b. Total Non-Federal Funds*	$0.00
c. Total Federal & Non-Federal Funds*	$11,650,521.00
d. Estimated Program Income*	$0.00

16.IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?*

a. YES ○ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:

DATE:

b. NO ● PROGRAM IS NOT COVERED BY E.O. 12372; OR

○ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

● I agree*

** The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.*

18. SFLLL or OTHER EXPLANATORY DOCUMENTATION File Name:

19. AUTHORIZED REPRESENTATIVE

Prefix: Dr. First Name*: Deborah Middle Name: Last Name*: Marshall Suffix: PhD
Position/Title*: AVP-ORSP
Organization Name*: Xavier University of Lousiana
Department: ORSP
Division: Office of the Provost
Street1*: 1 Drexel Drive
Street2:
City*: New Orleans
County:
State*: LA: Louisiana
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 70125-1098
Phone Number*: 504.520.5442 Fax Number: 504.520.7901 Email*: dmarsha2@xula.edu

Signature of Authorized Representative*
Deborah Marshall

Date Signed*
12/15/2017

20. PRE-APPLICATION File Name:

21. COVER LETTER ATTACHMENT File Name:

424 R&R and PHS-398 Specific
Table Of Contents

Component Summary

Components	Component Project Title	Organization Name	Contact PD/PI Name or Project Lead Name
Overall	Xavier RCMI Renewal Application-Overall	Xavier University of Lousiana	Wang, Guangdi
Admin-Core--001 (001)	Xavier RCMI Renewal Application-Administrative Core	Xavier University of Lousiana	Redacted by agreement
Core-001 (002)	Xavier RCMI Renewal Application--Community Engagement Core	Xavier University of Lousiana	
Core-002 (003)	Xavier RCMI Renewal Application-Investigator Development Core	Xavier University of Lousiana	
Core-003 (004)	Xavier RCMI Renewal Application-Research Infrastructure Core	Xavier University of Lousiana	
Project-001 (005)	Fostering informed-decision making about prostate cancer screening, diagnosis and treatment among clinicians and African American men	Xavier University of Lousiana	
Project-002 (006)	Developing an Orally Bioavailable SERD for Treatment of Metastatic/Advanced Breast Cancer	Xavier University of Lousiana	Wang, Guangdi
Project-003 (007)	A Data-driven Pan-Cancer Study of Biological Bases of Cancer Health Disparities	Xavier University of Lousiana	Redacted by agreement

Tracking Number: GRANT12536467 Funding Opportunity Number: RFA-MD-17-006. Received Date: 2017-12-15T12:15:48.000-05:00

Project/Performance
Site Location(s) Summary

Applicant Organization	City	State/Province	Country
Xavier University of Lousiana	New Orleans	LA	UNITED STATES

Organization Name	City	State/Province	Country	Component
Ochsner Clinic Foundation	New Orleans	LA	UNITED STATES	Project-001 (005)
Tulane University	New Orleans	LA	UNITED STATES	Project-001 (005)
Xavier University of Louisiana	New Orleans	LA	UNITED STATES	Admin-Core--001 (001)
Xavier University of Louisiana	New Orleans	LA	UNITED STATES	Core-001 (002)
Xavier University of Louisiana	New Orleans	LA	UNITED STATES	Overall
Xavier University of Louisiana	New Orleans	LA	UNITED STATES	Project-001 (005)
Xavier University of Louisiana	New Orleans	LA	UNITED STATES	Project-002 (006)
Xavier University of Louisiana	New Orleans	LA	UNITED STATES	Project-003 (007)
Xavier University of Lousiana	New Orleans	LA	UNITED STATES	Core-001 (002)
Xavier University of Lousiana	New Orleans	LA	UNITED STATES	Core-002 (003)
Xavier University of Lousiana	New Orleans	LA	UNITED STATES	Core-003 (004)

Human Subjects
Clinical Trials
Vertebrate Animals
HESC
Summary

Component	Human Subjects	Clinical Trial / Anticipated Clinical Trial	Vertebrate Animals	HESC
Overall	Y	N	Y	N
Admin-Core--001 (001)	N	N	N	N
Core-001 (002)	Y	N	N	N
Core-002 (003)	N	N	N	N
Core-003 (004)	N	N	N	N
Project-001 (005)	Y	N	N	N
Project-002 (006)	N	N	Y	N
Project-003 (007)	N	N	N	N

Tracking Number: GRANT12536467 Funding Opportunity Number: RFA-MD-17-006. Received Date:
2017-12-15T12:15:48.000-05:00

OMB No. 0925-0001 and 0925-0002 (Rev. 09/17 Approved Through 03/31/2020)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: **Guangdi Wang**

eRA COMMONS USER NAME (credential, e.g., agency login): Redacted by agreement

POSITION TITLE: **Professor of Chemistry**

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
East China Petroleum Institute	BS	1983	Chemical Engineering
University of New Orleans	MS	1994	Chemistry
University of New Orleans	Ph.D.	1995	Chemistry

A. Personal statement

Research in my laboratory in the past ten years has focused on three main areas: 1) therapeutic development for treatment of breast cancer, 2) drug metabolism and disposition, and 3) proteomic studies on mechanisms of drug action and for discovery of novel therapeutic targets in cancer. As demonstrated in my peer reviewed publications and current and past grant support, our laboratory has acquired a broad range of research expertise from design and synthesis of active compounds, analysis of their metabolism, in vitro and in vivo experiments testing their biological activities, to proteomic characterization of cellular alterations in response to drug action. Such preparations in laboratory research have positioned me well for serving as the Program Director for the proposed RCMI Program at Xavier. I am confident that my strong background in cancer research will allow me to provide the necessary leadership to push Xavier's cancer research program to a higher level in the next five years. We will see significant increase in quality publications and the number of funded R-series NIH grants. Xavier's RCMI Cancer Research Center was funded by NIMHD (August 1, 2009 – July 31, 2014) for which I am serving as the PI and Program Director. I played a key role in the planning and submitting the application and directing the program activities after the establishment of the Center. This is an important support mechanism for building Xavier's cancer research capabilities and strong collaborations and partnerships with local communities and stake holders in health disparity research. The experience in managing the current RCMI Cancer Research Center has prepared me well to serve as the PI/PD in the renewal application. In addition, my research background and expertise will enable my role as a faculty expert for the Research Infrastructure Core in topics ranging from drug design and synthesis, pharmacological, pharmcokinetic and metabolic studies, and proteomic investigations for cancer related research.

- Unpublished
- Zhang C, Guo S, Yang L, Liu J, Zheng S, Zhong, Zhang Q, **Wang G**, Metabolism, pharmacokinetics, and bioavailability of ZB716, a steroidal selective estrogen receptor downregulator (SERD), *Oncotarget*, **2017**, 8:103874-103889.
- Jiang Q, Zhong Q, Zhang Q, Zheng S, **Wang G**, Boron-based 4-hydroxytamoxifen bioisosteres for treatment of de novo tamoxifen resistance in breast cancer, *ACS Medicinal Chemistry Letters*, **2012**, 3 (5), 392–396.
- **Wang G**, Zhong Q, Zheng S, A boron-based prodrug strategy for increased bioavailablity and lower-dosage requirements for drug molecules containing at least one phenol (or aromatic hydroxyl) group, July

2, 2014, Application No. 62/020101. PCT application filed July 1, **2015** (PCT/US15/38768) WO2016004166A1

- **Wang G**, Liu J, Zheng S, Zhong Q, Guo S, Selective estrogen receptor down-regulators (serds), provisional patent filed May 6, **2016** (US 62/332,541), PCT filed May 5, **2017** (PCT/US17/31297).
- **Wang G**, Liu J, Zheng S, Guo S, Novel inhibitors of androgen receptor signaling, Provisional patent filed November 25, **2016** (US 62/426,368). PCT/US17/63004 filed Nov. 22, **2017**
- **Wang G**, Zheng S, Liu J, Zhong Q, Guo S, Boronic derivatives of hydroxamates as anticancer agents, Provisional patent filed November 29, **2016** (62/427,745), PCT/US17/63322, Nov. 27, **2017**.

B. Positions and Honors

1995 – 2001	**Assistant Professor** Department of Chemistry, Xavier University of Louisiana, New Orleans, LA
2001 – 2006	**Associate Professor** Department of Chemistry, Xavier University of Louisiana, New Orleans, LA
2006 – Present	**Professor of Chemistry** Department of Chemistry, Xavier University of Louisiana, New Orleans, LA
2006 – Present	**Program Member**, Louisiana Cancer Research Consortium, New Orleans, LA
2009 – Present	**Director, RCMI Cancer Research Center** Xavier University of Louisiana, New Orleans, LA
2006 – Present	**Adjunct Professor** Department of Structural and Cellular Biology, Tulane University School of Medicine, New Orleans, LA
2013	**Norman C. Francis Award for Excellence in Scholarship**

C. Contribution to Science

1. Addressing intrinsic resistance to tamoxifen therapy and potential risks of insufficient systemic level of active metabolites in patients with impaired CYP2D6 metabolism, my laboratory developed highly bioavailable boronic derivatives of 4-hydroxytamoxifen (ZB497) and endoxifen (ZB483) which are currently under further development for IND filing. We have found and reported that ZB497 and ZB483 demonstrated excellent pharmacological profiles of significantly greater bioavailability and in vivo efficacy as compared to either tamoxifen or direct administration of the metabolites, 4-hydroxytamoxifen and endoxifen. Following these two clinical trial candidates, we have recently developed ZB716, an orally bioavailable SERD, which has the potential to overcome the disadvantages associated with i.m. administration of fulvestrant, but more importantly can further increase the therapeutic efficacy and achieve more durable treatment outcome than the current SERD regimen.
    a. Zhang C, Zhong Q, Zhang Q, Zheng S, Miele L, **Wang G**, Boronic prodrug of endoxifen prodrug as an effective hormone therapy for breast cancer, *Breast Cancer Res. Treat*., **2015**, Jul;152(2):283-91. doi: 10.1007/s10549-015-3461-9.
    b. Zhong Q, Zhang C, Zhang Q, Zheng S, Miele L, **Wang G**, Boronic prodrug of 4-hydroxytamoxifen is more efficacious than tamoxifen in inhibiting ER+ breast tumor in vivo, *BMC Cancer*, **2015,**15:625, DOI 10.1186/s12885-015-1621-2.
    c. Liu J, Zheng S, Akerstrom VL, Yuan C, Ma Y, Zhong Q, Zhang C, Zhang Q, Guo S, Ma P, Skripnikova EV, Pannuti A, Miele L, Wiese TE, **Wang G**, Fulvestrant-3 boronic acid (ZB716): an orally bioavailable selective estrogen receptor downregulator (SERD), *Journal of Medicinal Chemistry*, **2016**, Sep 8;59(17):8134-40.
    d. Liu J, Zheng S, Guo S, Zhang C, Zhong Q, Zhang Q, Ma P, Skripnikova EV, Bratton MR, Wiese TE, **Wang G**, Rational design of a boron-modified triphenylethylene (GLL398) as an orally bioavailable non-steroidal selective estrogen receptor downregulator (SERD), *ACS Med Chem Lett*, **2017**, *8* (1), pp 102–106

2. Therapeutic development research in my laboratory has also focused on other types of small molecule oncology drug discovery including HDAC inhibitors, anti-migration inhibitors, anti-vasculature agents, and novel chemical entities with anti-prostate cancer activities.

a. Unpublished

b. Unpublished

c. Zheng S, Zhong Q, He L, Mottamal M, Sridhar J, Zhang Q, **Wang G**. Modification and Biological Evaluation of Thiazole Derivatives as Novel Inhibitors of Metastatic Cancer Cell Migration and Invasion, *Journal of Medicinal Chemistry*, **2014**, 14;57(15):6653-67. doi: 10.1021/jm500724x. PMC4136724.

d. Zheng S, Zhong Q, Mottamal M, Zhang C, Lemelle E, McFerrin H, Zhang Q, **Wang G**. Design, Synthesis, and Biological Evaluation of Novel Pyridine-Bridged Analogs of Combretastatin-A4 as Anti-cancer Agents, *Journal of Medicinal Chemistry*, **2014**, 57(8):3369-81.

3. Proteomics is now at the forefront of nearly all branches of biomedical research. It has brought about new ways of conducting molecular biology research and will continue to transform the way information and data are collected. Proteomics provides an unbiased, holistic view of biological systems that can reveal hitherto unknown causal elements underlying various pathologies. In particular, my laboratory has utilized proteomics as an exploratory tool to study mechanisms of drug resistance in cancer cells by quantitatively analyzing proteomic changes in the resistant phenotypes. We have identified and validated several resistance-enabling or resistance-associated proteins. Importantly, we have discovered that an actin bundling protein, fascin, can be a therapeutic target to block cancer cell migration and invasion. Further efforts in drug design and development led to the discovery of thiazole analogs that potently inhibited the migratory and invasive behavior of cancer cells with minimal cytotoxicities. These compounds may serve as promising leads for pre-clinical development of anti-migration and anti-invasion therapeutics.
   a. Zhou C, Nitschke AM, Xiong W, Zhang Q, Tang Y, Bloch M, Elliott S, Zhu Y, Bazzone L, Yu D, Weldon CB, Schiff R, McLachlan JA, Beckman BS, Wiese TE, Nephew KP, Shan B, Burow ME, **Wang G**. Proteomic analysis of tumor necrosis factor-α resistant human breast cancer cells reveals a MEK5/Erk5-mediated epithelial-mesenchymal transition phenotype, **2008**, *Breast Cancer Res.* 10(6):R105.
   b. Zhou C, Zhong Q, Rhodes LV, Townley I, Bratton MR, Zhang Q, Martin EC, Elliott S, Collins-Burow BM, Burow ME, **Wang G**. Proteomic analysis of acquired tamoxifen resistance in MCF-7 cells reveals expression signatures associated with enhanced migration. *Breast Cancer Res***. 2012** Mar 14;14(2):R45.
   c. Tilghman SL, Townley I, Zhong Q, Carriere PP, Zou J, Llopis SD, Preyan LC, Williams CC, Skripnikova E, Bratton MR, Zhang Q, **Wang G**. Proteomic signatures of acquired letrozole resistance in breast cancer: suppressed estrogen signaling and increased cell motility and invasiveness. *Mol Cell Proteomics*. **2013** Sep;12(9):2440-55.
   d. Guo S, Zou J, **Wang G**. Advances in the proteomic discovery of novel therapeutic targets in cancer. *Drug Design, Development, and Therapy*. **2013**, 7:1259-71.

4. Drug metabolism study is an integral part of therapeutics discovery and development. From 2000 to 2005 My laboratory devoted significantly amount of time and resources to analytical method validation and optimization for identification and quantification of various drug metabolites, in particular, of synthetic cannabinoid receptor ligands. Our foundational work in this field has elucidated many unknown metabolic pathways based on an in vitro liver microsomal model and the analytical platform of HPLC-MS/MS.
   a. Zhang Q, Ma P, Cole RB, **Wang G**: "In vitro metabolism of JWH-015, an aminoalkylindole agonist for the peripheral cannabinoid receptor, *Anal Bioanal Chem,* **2006**, 386:1345-1355.
   b. Zhang Q, Ma P, Iszard M, Cole RB, Wang W, **Wang G**. In vitro metabolism of R(+)-[2,3-dihydro -5-methyl-3-[(morpholinyl)methyl]pyrrolo [1,2,3-de]1,4-benzoxazinyl]-(1-naphthalenyl) methanone mesylate, a cannabinoid receptor agonist. *Drug Metab Dispos*. **2002**, 30(10):1077-86.
   c. Zhang Q, Ma P, Wang W, Cole RB, **Wang G**. In vitro metabolism of diarylpyrazoles, a novel group of cannabinoid receptor ligands. *Drug Metab Dispos*. **2005**, 33(4):508-17.

d. Zhang Q, Ma P, Cole RB, **Wang G**. In vitro metabolism of indomethacin morpholinylamide (BML-190), an inverse agonist for the peripheral cannabinoid receptor (CB(2)) in rat liver microsomes. *Eur J Pharm Sci*. **2010**, 41(1):163-72.

5. My doctoral research contributed to the fundamental understanding of the mechanism of electrospray ionization (ESI), at a time when ESI was gaining wide acceptance as an ideal ionization method for polar and large molecules previously inaccessible to mass spectrometric analysis. As illustrated in the publications listed below, I studied systematically how various factors such as solvent polarity, analyte concentration, type of counterions, and gas-phase acidity and basicity influence the ionization efficiency and charge-state distribution of the ESI generated ions. This body of work made significant contributions to our current understanding of the electrospray ionization processes.
   a. **Wang G**, Cole RB, Effects of solvent and counterion on ion-pairing and observed charge states of diquaternary ammonium salts in electrospray ionization mass spectrometry" *J Am Soc Mass Spectrom.* **1996**, 7:1050-1058.
   b. **Wang G**, Cole RB, Mechanistic interpretation of the dependence of charge state distributions on analyte concentrations in electrospray mass spectrometry, *Anal Chem*, **1995**, 67:2892-2900.
   c. **Wang G**, Cole RB, Effect of solution ionic strength on analyte charge state distributions in positive and negative ion electrospray mass spectrometry, *Analytical Chemistry* **1994**, 66:3702-3708.
   d. **Wang G**, Cole RB, Disparity between solution phase equilibria and charge state distributions in positive ion electrospray mass spectrometry, *Organic Mass Spectrometry*. **1994**, 29:419-427.

A Partial List of Published Work and Patents in MyBibliography can be found at:
http://www.ncbi.nlm.nih.gov/sites/myncbi/guangdi.wang.1/bibliography/48501011/public/?sort=date&direction=descending

D. Research Support.

Current Support

2G12MD007595 8/1/2014 – 3/31/2019
NIH-NIMHD
RCMI Cancer Research Center at Xavier University of Louisiana
The goals of Xavier's proposed RCMI Cancer Research Center are to continue to build on and enhance faculty competitiveness and the University's strengths in cancer and health disparities research in a manner that will not only lead to exciting new discoveries, but also intensify Xavier's efforts to translate the results of these activities to the benefit of the public, particularly the underserved.
Role: PI and Program Director

1R43CA213462
IND-enabling Studies of ZB716, an Orally Bioavailable SERD 4/1/2017 – 1/31/2018
NIH-NCI
The goals of this project is to develop a potent, orally bioavailable selective estrogen receptor degrader (SERD) that can be used as a second-line endocrine regimen for patients with progressive metastatic ER-positive breast cancer.
Role: Principal Investigator

Completed Projects

Louisiana Cancer Research Consortium Seed Grant 7/1/2011 – 12/31/2015
Developing a quantitative phosphoproteomics method for breast cancer research
The goal of this seed grant is to develop optimal working protocols for cellular phosphoproteomic analysis for breast cancer research.
Role: PI

Louisiana Clinical and Translational Science Center Pilot Project 10/1/2013 – 12/31/2015
Boron-based 4-Hydroxytamoxifen and Endoxifen Prodrugs for Treatment of Breast Cancer

The goal of this pilot project is to conduct preclinical studies of boron-4OHT and boron-endoxifen to determine the *in vivo* efficacy and pharmacokinetics.
Role: PI

1G12RR026250 8/1/2009 – 7/31/2014
NIH-NCRR
Xavier's RCMI Cancer Research Program
The goals of Xavier's proposed RCMI program are to enhance university-wide cancer research infrastructure and faculty research competitiveness by establishing core laboratories, providing startup funds for newly hired faculty with cancer research projects, and supporting pilot research projects.
Role: Program Director

59-6435-8-317 7/1/2009 – 9/30/2012
USDA
Design and Synthesis of Isoflavone and Glyceollin Derivatives as Potential Antagonists for the Estrogen Receptor
The Goal of the proposed research is to design, synthesize, and evaluate biological activities of various phytoestrogen analogues. The long term goal is to find potent estrogen receptor antagonists that have anti-estrogen and anti-proliferation properties against breast cancer.
Role: Subproject PI

Summary

To sustain Xavier's overall research momentum, enhance research capacity, and advance to the next level of excellence in biomedical research on minority health and health disparities, the RCMI Cancer Research Center will implement program activities to support early stage, underrepresented investigators, maintain core facilities to support Xavier researchers at all levels of career development, and to promote and sustain long-lasting, bidirectional partnerships between Xavier and local communities to address cancer health disparities. The proposed RCMI Center will consist of three major research projects in two areas: basic biomedical research and behavioral research, and 4 Cores: the Administrative Core, the Investigator Development Core, the Research Infrastructure Core, and the Community Engagement Core. These programs will be implemented to achieve the following specific aims: Aim 1. Enhance Xavier's research capacity for basic biomedical and behavioral research. The RCMI program will maintain, strengthen and optimize core services in support of Xavier investigators. Core facilities will be restructured, consolidated, and operations will be streamlined to maximize productivity and efficiency of Xavier's ongoing research projects. Aim 2. Enable Xavier investigators to become more competitive in obtaining external funding. This will be achieved by 1) supporting *two research projects in the basic biomedical area and one research project in the behavioral research area* to enable these project PIs to become competitive in R01 applications; 2) providing critical research resources such as shared state-of-the-art instrumentation required in a competitive research project through the *Research Infrastructure Core*; 3) providing, through *the Investigator Development Core,* pilot funding to obtain necessary preliminary data for development of fundable research proposals; and 4) providing grantsmanship training through grant writing workshops and professional review services. Aim 3. Promote career enhancement of Xavier's new and early stage investigators through a pilot project fund and by initiating a research/grantsmanship "pipeline" supporting new faculty for five years to obtain extramural funding. Aim 4. Enhance the quality of all scientific inquiry and promote research on minority health and health disparities by semi-annual symposiums and workshops on the quality of minority health and health disparities research each year to offer training in good scientific practices, appropriate statistical usage, and responsible laboratory practices for researchers at all levels. Working through the *Community Engagement Core* and the *Investigator Development Core*, the RCMI program will foster close interactions and collaborations among basic and behavior researchers, clinicians, and community stakeholders. Aim 5. Establish sustainable relationships with community-based organizations that will partner with Xavier researchers. A *Community Engagement Core* will be established to 1) promote and sustain community-academic partnerships through bidirectional knowledge sharing on intervention strategies and scientific discovery in cancer health disparities; 2) facilitate greater community involvement in setting research priorities and creating more opportunities for academic-practitioner-community research partnerships; 3) build capacity (knowledge and skills) among research investigators, community members, health systems, and potential research participants to conduct innovative and transformative research that addresses community health needs; 4) provide support for investigators to better disseminate research findings to the scientific community, community organizations, and lay communities.

OMB Number: 4040-0001
Expiration Date: 10/31/2019

APPLICATION FOR FEDERAL ASSISTANCE

SF 424 (R&R)

5. APPLICANT INFORMATION **Organizational DUNS*:** 020857876

Legal Name*: Xavier University of Lousiana
Department:
Division:
Street1*: 1 Drexel Drive
Street2:
City*: New Orleans
County: Orleans
State*: LA: Louisiana
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 70125-1098

Person to be contacted on matters involving this application

Prefix:	First Name*:	Middle Name:	Last Name*:	Suffix:
Dr.	Dangale		Meda	PhD

Position/Title: Asst. VP-ORSP
Street1*: 1 Drexel Drive
Street2:
City*: New Orleans
County: Orleans
State*: LA: Louisiana
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 70125-1098
Phone Number*: 504.520.5600 Fax Number: 504.520.7901 Email: dmeda@xula.edu

7. TYPE OF APPLICANT* T: Historically Black Colleges and Universities (HBCUs)

Other (Specify):

Small Business Organization Type ❍ Women Owned ❍ Socially and Economically Disadvantaged

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*
Developing an Orally Bioavailable SERD for Treatment of Metastatic/Advanced Breast Cancer

12. PROPOSED PROJECT

Start Date*	Ending Date*
09/15/2018	09/14/2023

OMB Number: 4040-0010
Expiration Date: 10/31/2019

Project/Performance Site Location(s)

Project/Performance Site Primary Location

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:	Xavier University of Louisiana
Duns Number:	020857876
Street1*:	1 Drexel Drive
Street2:	
City*:	New Orleans
County:	
State*:	LA: Louisiana
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	70125-1098
Project/Performance Site Congressional District*:	LA-002

Additional Location(s) File Name:

Funding Opportunity Number: RFA-MD-17-006. Received Date: 2017-12-15T12:15:48.000-05:00

OMB Number: 4040-0001
Expiration Date: 10/31/2019

RESEARCH & RELATED Other Project Information

1. Are Human Subjects Involved?* ❍ **Yes** ● **No**

1.a. If YES to Human Subjects

Is the Project Exempt from Federal regulations? ❍ Yes ❍ No

If YES, check appropriate exemption number: _ 1 _ 2 _ 3 _ 4 _ 5 _ 6

If NO, is the IRB review Pending? ❍ **Yes** ❍ **No**

IRB Approval Date:

Human Subject Assurance Number

2. Are Vertebrate Animals Used?* ● **Yes** ❍ **No**

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? ● Yes ❍ No

IACUC Approval Date:

Animal Welfare Assurance Number A3024-01

3. Is proprietary/privileged information included in the application?* ❍ **Yes** ● **No**

4.a. Does this project have an actual or potential impact - positive or negative - on the environment?* ❍ **Yes** ● **No**

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? ❍ Yes ❍ No

4.d. If yes, please explain:

5. Is the research performance site designated, or eligible to be designated, as a historic place?* ❍ **Yes** ● **No**

5.a. If yes, please explain:

6. Does this project involve activities outside the United States or partnership with international collaborators?* ❍ **Yes** ● **No**

6.a. If yes, identify countries:

6.b. Optional Explanation:

	Filename
7. Project Summary/Abstract*	Project_Summary1001356363.pdf
8. Project Narrative*	Project_Narrative_final1001356364.pdf
9. Bibliography & References Cited	Bibliography1001356365.pdf
10.Facilities & Other Resources	Facilities_and_other_resources1001356366.pdf
11.Equipment	

Funding Opportunity Number: RFA-MD-17-006. Received Date: 2017-12-15T12:15:48.000-05:00

Project Summary

Selective estrogen receptor downregulators (SERDs) are a class of endocrine therapy agents that act both as estrogen receptor (ER) antagonists and ER degraders effective in treating metastatic or advanced breast cancer that disproportionately affects African American women. Fulvestrant is the only FDA approved SERD indicated for advanced or metastatic breast cancer both as a first line and second line endocrine agent. However, this injection only drug is poorly bioavailable and it takes 30 days to reach its maximal steady-state plasma concentration, limiting the clinical response rate to lower than 20% in the hormone resistant setting. An oral SERD with greater drug exposure and faster action would bring immediate clinical benefits to patients with advanced breast cancer. Further, in light of the recent FDA approval of fulvestrant as a combination therapy with CDK4/6 inhibitor palbociclib for advanced breast cancer, the clinical utility of an oral SERD in the combination treatment setting is also very significant. Advances in oral SERDs development have been limited to nonsteroidal molecules with several being currently evaluated in phase 1 clinical trials, yet none has advanced to phase II clinical trials. Our lead compound, ZB716, has shown promising preclinical data in bioavailability, efficacy, and toxicology. ZB716 binds to ER with high affinity and exerts its antiestrogenic effect on ER-expressing breast cancer cells. In both tamoxifen naive and tamoxifen resistant breast cancer cells, ZB716 potently inhibits cell proliferation and effectively degrades the hormone receptor in a dose-dependent manner. In animals, we have shown that ZB716 has far superior oral bioavailability when compared to fulvestrant. Moreover, in direct comparison to the two oral SERDs under clinical trials, ZB716 is a stronger antiestrogen and ER-degrader. To further advance the preclinical development of ZB716 we propose to investigate the in vivo efficacy of ZB716 in endocrine resistant, patient derived breast tumor models that most closely resemble clinical settings for which SERD is indicated. We will also evaluate ZB716 efficacy in combination with a CDK4/6 inhibitor, palbociclib and investigate the mechanism of action of ZB716 on patient-derived xenografts (PDX) expressing mutant forms of ER and determine the binding behavior of ZB716 to mutant ERs and its modulation of ERα-coregulator interactions. Finally, we will determine optimal reaction conditions under which ZB716 can be prepared in larger scale, investigate its physical properties and formulation options for toxicological studies in animals, and conduct metabolic profiling, pharmacokinetics, and bioavailability studies. Accomplishing the proposed studies will provide key efficacy data to determine whether ZB716 is effective in treating endocrine resistant, ESR1 mutant breast cancer and whether it is a true antiestrogen and ER degrader by acting through the ER. The studies will also demonstrate the clinical utility of ZB716 as a combination therapy when used with a CDK4/6 inhibitor. Moreover, synthetic method optimization will pave the way for scalable manufacture of the API, and safety pharmacology and physical chemical properties will fulfill IND-enabling data. In summary, the proposed research will advance this promising oral SERD towards clinical trials to test its safety and efficacy in breast cancer patients.

Project Narrative

Developing orally bioavailable selective estrogen receptor degraders (SERDs) to improve therapeutic efficacy for breast cancer patients is an ongoing effort. The proposed studies will determine if our lead SERD candidate is effective in patient derived xenograft breast tumor models that resemble clinical settings for which SERD is indicated, optimize method of preparation of the drug candidate, and obtain preclinical data before the drug can be tested in the clinic.

FACILITIES & OTHER RESOURCES

Xavier University of Louisiana

The PI and his research team can count on a research environment at Xavier that is strongly supportive of the proposed research. The PI has full access to the state-of-the-art mass spectrometry facility consisting of a state-of-the-art HPLC-MS/MS instrument (Thermo TSQ Vantage), two linear trap mass spectrometers and one high resolution Orbitrap tandem mass spectrometer for the identification and quantification of the prodrugs and related compounds in plasma and tumor tissues proposed in this application. In addition to a fully equipped molecular biology laboratory (see descriptions below) designated for use by the PI, complementary resources are available to the PI that include a Drug Discovery and Delivery Core Laboratory, Major Instrumentation Core Laboratory, and a Cell and Molecular Biology Core Laboratory operated by Xavier's RCMI Cancer Research Program. As a Louisiana Cancer Research Consortium member, the PI works in a rich intellectual environment with several ongoing collaborations with other extramurally funded investigators using proteomics as a research platform. These available resources provide a scientific environment that will be highly conducive to the successful implementation of the proposed research project.

Xavier's Animal Research Facility

Xavier University of Louisiana has enhanced and expanded its Laboratory Animal Research capability by building an Redacted by agreement Animal Research Facility in the Redacted by agreement This facility includes specialized animal research rooms and modern animal care technologies. The animal facility will support the University's commitment to biomedical research and the Xavier strategic plan for expansion of the University's biomedical research program. One key objective in the plan is to enhance the ability of science faculty, and students with modern facilities. The second objective is to place the University in a competitive position among the Greater New Orleans Area Research Institutions.

The animal facility now offers 52 % Animal Research Space verses 48% Non-Research Space for our faculty and students to conduct laboratory animal research. The design and size of the facility will allow for excellent animal management and human comfort and health protection. The animals are housed in rooms dedicated to or assigned for that purpose and will not be in laboratories merely for convenience. The addition of a CRi Maestro multispectral small animal imager in the animal facility now allows in vivo imaging of tumors and organs without the need for surgery, offers fast and accurate in vivo analysis, and dramatically decreases the number of animals to be sacrificed.

Laboratory:

1. Research Lab 304: located in Xavier's NCF Building. This laboratory has approximately 400 sq Ft and will be used primarily for preparation of reagent solutions and HPLC mobile phases, and standard solutions. There are two refrigerators and freezers for reagent and sample storage.
2. Synthetic Research Lab NCF 372: located in NCF Building. This laboratory has approximately 500 sq Ft and will be used primarily for synthetic scale up and process optimization.
3. Research Lab 311: located in Xavier's Pharmacy Building. This laboratory has approximately 450 sq Ft assigned for cell culture and proteomics related experiments such as gel electrophoresis, imaging, protein digesting, isobaric labeling, fractionation, and lyophilizing.
4. RCMI Core Facility Rm 425: located in Xavier's Pharmacy Building. This newly renovated core laboratory currently houses the Thermo Vantage HPLC-MS/MS instrument and the Thermo nano-LC-LTQ-Orbitrap MS instrument.

Office:

1. Office 339: located in Xavier's NCF Building. This is PI's main office in the Chemistry Department.
2. Office 305A: located in Xavier's NCF Building. This is used as the office for research staff in PI's laboratory

Computers and Software for Data Processing and Bioinformatics:

1. Dell desktops (5) – Rm 304, 305A, 311
2. HP lab tops (3) – One each used by PI and two research staff
3. HP Z400 Workstation (1) located in Lab 320. This fast computer is used for proteomics data processing and statistical analysis.
4. MASCOT proteomics search engine, installed on the HP Z400 Workstation.
5. Sequest proteomics search engine, installed on the HP Z400 Workstation.

OTHER

Xavier offers an excellent research environment conducive to the scope and goals of the proposed project.

1. In 2007 Xavier University became one of the three partner institutes (the other two being Tulane University Cancer Center and Louisiana State University Health Sciences Center) of the Louisiana Cancer Research Consortium (LCRC). As an active program member, the PI has enjoyed extensive collaborative opportunities with researchers from the LCRC. The PI has received funds from LCRC to purchase proteomics equipment for use by Xavier researchers and those from Tulane and LSU.
2. In addition, Xavier University received funds in 2009 to establish a Research Centers in Minority Institutions (RCMI) program focusing on enhancing the cancer research competitiveness of Xavier researchers, and again in 2014 to continue the operation of the RCMI Cancer Research Center. As Program Director, the PI oversees the implementation of the RCMI program goals while having full access to the Drug Discovery and Delivery Core, the proteomic core facilities and molecular biology core services. These facilities have been extremely helpful for the PI to obtain preliminary data for this application.

Equipment:

- Reactors: 1, 3, 5, 10, and 20 L Jacketed Reactors (-45 °C to +190 °C)
- Industrial vacuum drying ovens
- Büchi Evaporator R-220R
- Labconco Freeze Dry System,
- Autopol IV Polarimeter
- Analytical and preparative HPLC Waters Alliance units and automated flash chromatography equipment ISCO Teledyne Combiflash Companion Rf
- Large scale Companion XL, Büchi rotary evaporators
- Solvent purification/drying system PureSolv™
- Analytical and technical balances
- 300 MHz and 400 MHz Bruker NMR spectrophotometer
- FTIR Perkin Elmer Spectrum One ES System
- Discoverer automated microwave synthesizers (2)
- Radleys Stacker SPE purification stations (2)
- Gilson 215 liquid handlers
- Genevac EZ-2 parallel evaporator
- UPLC with PDA, ELSD, and MS (ZQ) detectors;
- Thermo TSQ Vantage triple quadrupole tandem mass spectrometer equipped with UHPLC system.
- Thermo Q-Exactive Orbitrap high resolution MS equipped with UHPLC system

OMB Number: 4040-0001
Expiration Date: 10/31/2019

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix: Dr. First Name*: Guangdi Middle Name Last Name*: Wang Suffix: PhD

Position/Title*: Professor
Organization Name*: Xavier University of Lousiana
Department: Chemistry
Division: Div. of Math. & Phys.Sciences
Street1*: 1 Drexel Drive
Street2:
City*: New Orleans
County:
State*: LA: Louisiana
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 70125-1098

Phone Number*: 504.520.5076 Fax Number: 504.520.7942

E-Mail*: gwang@xula.edu

Credential, e.g., agency login: eRA Commons User Name

Project Role*: Other (Specify) Other Project Role Category: Project PI

Degree Type: PhD Degree Year: 1995

Attach Biographical Sketch*: File Name:

Attach Current & Pending Support: File Name:

Tracking Number: GRANT12536467
Funding Opportunity Number: RFA-MD-17-006 . Received Date: 2017-12-15T12:15:48.000-05:00

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 1

ORGANIZATIONAL DUNS*: 020857876

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: Xavier University of Lousiana

Start Date*: 09-15-2018 **End Date*:** 09-14-2019 **Budget Period: 1**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1.	Dr.	Guangdi		Wang	PhD	Project PI	Institutional Base Salary	EFFORT	EFFORT	EFFORT	29,373.00	6,462.00	35,835.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **35,835.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
2	Research Scientists	24			110,000.00	24,200.00	134,200.00
2	**Total Number Other Personnel**					**Total Other Personnel**	**134,200.00**
					Total Salary, Wages and Fringe Benefits (A+B)		**170,035.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Tracking Number: GRANT12536467
Funding Opportunity Number: RFA-MD-17-006. Received Date: 2017-12-15T12:15:48.000-05:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 1

ORGANIZATIONAL DUNS*: 020857876
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: Xavier University of Lousiana

Start Date*: 09-15-2018 **End Date*:** 09-14-2019 **Budget Period: 1**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	
Additional Equipment: File Name:	

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	4,000.00
2. Foreign Travel Costs	
Total Travel Cost	**4,000.00**

E. Participant/Trainee Support Costs	**Funds Requested ($)***
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees **Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 1

ORGANIZATIONAL DUNS*: 020857876
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: Xavier University of Lousiana

Start Date*: 09-15-2018 **End Date*:** 09-14-2019 **Budget Period: 1**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	35,000.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Vivarium Costs	50,000.00
Total Other Direct Costs	**85,000.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**259,035.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1. On Campus _ Salaries & Wages	65.5	146,111.00	95,703.00
		Total Indirect Costs	**95,703.00**

Cognizant Federal Agency DHHS
(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**354,738.00**

J. Fee	Funds Requested ($)*

K. Budget Justification* File Name:
Budget_justification1001356484.pdf
(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

Funding Opportunity Number: RFA-MD-17-006. Received Date: 2017-12-15T12:15:48.000-05:00

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 2

ORGANIZATIONAL DUNS*: 020857876

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: Xavier University of Lousiana

Start Date*: 09-15-2019 **End Date*:** 09-14-2020 **Budget Period: 2**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1.	Dr.	Guangdi		Wang	PhD	Project PI	Institutional Base Salary	EFFORT	EFFORT	EFFORT	30,254.00	6,656.00	36,910.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **36,910.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
2	Research Scientists	24			113,300.00	24,926.00	138,226.00
2	**Total Number Other Personnel**					**Total Other Personnel**	**138,226.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**175,136.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Tracking Number: GRANT12536467
Funding Opportunity Number: RFA-MD-17-006. Received Date: 2017-12-15T12:15:48.000-05:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 2

ORGANIZATIONAL DUNS*: 020857876
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: Xavier University of Lousiana

Start Date*: 09-15-2019 **End Date*:** 09-14-2020 **Budget Period: 2**

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	4,000.00
2. Foreign Travel Costs	
Total Travel Cost	**4,000.00**

E. Participant/Trainee Support Costs	**Funds Requested ($)***
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees **Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 2

ORGANIZATIONAL DUNS*: 020857876
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: Xavier University of Lousiana

Start Date*: 09-15-2019 **End Date*:** 09-14-2020 **Budget Period: 2**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	20,076.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Vivarium Costs	36,155.00
Total Other Direct Costs	**56,231.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**235,367.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1. On Campus _ Salaries & Wages	65.5	150,494.00	98,574.00
		Total Indirect Costs	**98,574.00**

Cognizant Federal Agency DHHS
(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**333,941.00**

J. Fee	Funds Requested ($)*

K. Budget Justification* File Name:
Budget_justification1001356484.pdf
(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

Funding Opportunity Number: RFA-MD-17-006. Received Date: 2017-12-15T12:15:48.000-05:00

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 3

ORGANIZATIONAL DUNS*: 020857876

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: Xavier University of Lousiana

Start Date*: 09-15-2020 **End Date*:** 09-14-2021 **Budget Period: 3**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1.	Dr.	Guangdi		Wang	PhD	Project PI	Institutional Base Salary	EFFORT	EFFORT	EFFORT	31,161.00	6,855.00	38,016.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **38,016.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
2	Research Scientists	24			116,699.00	25,674.00	142,373.00
2	**Total Number Other Personnel**					**Total Other Personnel**	**142,373.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**180,389.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Tracking Number: GRANT12536467
Funding Opportunity Number: RFA-MD-17-006. Received Date: 2017-12-15T12:15:48.000-05:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 3

ORGANIZATIONAL DUNS*: 020857876
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: Xavier University of Lousiana

Start Date*: 09-15-2020 **End Date*:** 09-14-2021 **Budget Period: 3**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	
Additional Equipment: File Name:	

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	2,250.00
2. Foreign Travel Costs	
Total Travel Cost	**2,250.00**

E. Participant/Trainee Support Costs	**Funds Requested ($)***
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees **Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Funding Opportunity Number: RFA-MD-17-006. Received Date: 2017-12-15T12:15:48.000-05:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 3

ORGANIZATIONAL DUNS*: 020857876
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: Xavier University of Lousiana

Start Date*: 09-15-2020 **End Date*:** 09-14-2021 **Budget Period: 3**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	9,880.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Vivarium Costs	31,207.00
Total Other Direct Costs	**41,087.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**223,726.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1. On Campus _ Salaries & Wages	65.5	155,009.00	101,531.00
		Total Indirect Costs	**101,531.00**

Cognizant Federal Agency DHHS
(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**325,257.00**

J. Fee	Funds Requested ($)*

K. Budget Justification* File Name:
Budget_justification1001356484.pdf
(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

Funding Opportunity Number: RFA-MD-17-006. Received Date: 2017-12-15T12:15:48.000-05:00

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 4

ORGANIZATIONAL DUNS*: 020857876

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: Xavier University of Lousiana

Start Date*: 09-15-2021 **End Date*:** 09-14-2022 **Budget Period: 4**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1.	Dr.	Guangdi		Wang	PhD	Project PI	Institutional Base Salary	EFFORT	EFFORT	EFFORT	32,096.00	7,061.00	39,157.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **39,157.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
2	Research Scientists	24			120,200.00	26,444.00	146,644.00
2	**Total Number Other Personnel**					**Total Other Personnel**	**146,644.00**
					Total Salary, Wages and Fringe Benefits (A+B)		**185,801.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Tracking Number: GRANT12536467
Funding Opportunity Number: RFA-MD-17-006. Received Date: 2017-12-15T12:15:48.000-05:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 4

ORGANIZATIONAL DUNS*: 020857876
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: Xavier University of Lousiana

Start Date*: 09-15-2021 **End Date*:** 09-14-2022 **Budget Period: 4**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	
Additional Equipment: File Name:	

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	2,250.00
2. Foreign Travel Costs	
Total Travel Cost	**2,250.00**

E. Participant/Trainee Support Costs	**Funds Requested ($)***
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees **Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Funding Opportunity Number: RFA-MD-17-006. Received Date: 2017-12-15T12:15:48.000-05:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 4

ORGANIZATIONAL DUNS*: 020857876
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: Xavier University of Lousiana

Start Date*: 09-15-2021 **End Date*:** 09-14-2022 **Budget Period: 4**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	10,750.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Vivarium Costs	27,668.00
Total Other Direct Costs	**38,418.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**226,469.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1. On Campus _ Salaries & Wages	65.5	159,660.00	104,577.00
		Total Indirect Costs	**104,577.00**

Cognizant Federal Agency DHHS
(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**331,046.00**

J. Fee	Funds Requested ($)*

K. Budget Justification* File Name:
Budget_justification1001356484.pdf
(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

Funding Opportunity Number: RFA-MD-17-006. Received Date: 2017-12-15T12:15:48.000-05:00

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 5

ORGANIZATIONAL DUNS*: 020857876

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: Xavier University of Lousiana

Start Date*: 09-15-2022 **End Date*:** 09-14-2023 **Budget Period: 5**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1.	Dr.	Guangdi		Wang	PhD	Project PI	Institutional Base Salary	EFFORT	EFFORT	EFFORT	33,059.00	7,273.00	40,332.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **40,332.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
2	Research Scientists	24			123,806.00	27,237.00	151,043.00
2	**Total Number Other Personnel**					**Total Other Personnel**	**151,043.00**
					Total Salary, Wages and Fringe Benefits (A+B)		**191,375.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Tracking Number: GRANT12536467
Funding Opportunity Number: RFA-MD-17-006. Received Date: 2017-12-15T12:15:48.000-05:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 5

ORGANIZATIONAL DUNS*: 020857876
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: Xavier University of Lousiana

Start Date*: 09-15-2022 **End Date*:** 09-14-2023 **Budget Period: 5**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	
Additional Equipment: File Name:	

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	4,000.00
2. Foreign Travel Costs	
Total Travel Cost	**4,000.00**

E. Participant/Trainee Support Costs	**Funds Requested ($)***
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees **Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Funding Opportunity Number: RFA-MD-17-006. Received Date: 2017-12-15T12:15:48.000-05:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 5

ORGANIZATIONAL DUNS*: 020857876
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: Xavier University of Lousiana

Start Date*: 09-15-2022 **End Date*:** 09-14-2023 **Budget Period: 5**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	13,760.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Vivarium Costs	32,211.00
Total Other Direct Costs	**45,971.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**241,346.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1. On Campus _ Salaries & Wages	65.5	164,451.00	107,715.00
		Total Indirect Costs	**107,715.00**

Cognizant Federal Agency DHHS
(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**349,061.00**

J. Fee	Funds Requested ($)*

K. Budget Justification* File Name:
Budget_justification1001356484.pdf
(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

Funding Opportunity Number: RFA-MD-17-006. Received Date: 2017-12-15T12:15:48.000-05:00

Program Director/Principal Investigator (Last, First, Middle): Wang, Guangdi

Budget Justification

Personnel

Guangdi Wang, Ph.D. – Principal Investigator (EFFORT)

As PI of the project, Dr. Wang will devote EFFORT of his effort to managing and implementing the preclinical studies of ZB716 as proposed in this application. He will be responsible for recruiting the two research associates to conduct synthesis and pharmacology work, overseeing all research progress, and disseminating findings in publications and scientific conferences. Dr. Wang will also be responsible for ensuring regulatory compliance with animal protocols and communicating with contract research laboratories for non-rodent experiments proposed in the application.

The budget requested for Guangdi Wang's EFFORT is $29,373 for the first year, with 3% increase in subsequent years.

Research associate – Medicinal or Process Chemist (12 calendar mos.)

The full time medicinal chemist or process chemist will be responsible for synthesis of ZB716, process optimization, and physical properties measurements. The chemist will prepare up to 100 g of purified ZB716 for no-GLP animal studies and other proposed assays.

The budget requested for the full time chemist is $55,000, with 3% increase in each of the subsequent years.

Research associate – Pharmacologist. (12 calendar mos.)

The full-time pharmacologist will be responsible for efficacy studies of ZB716 in patient derived xenograft breast cancer models where ZB716 will be tested as a single agent and as a combination therapy with palbociclib (CDK4/6 inhibitor). The pharmacologist will also conduct pharmacokinetic studies in rodents at Xavier University's animal facilities. Additional work includes proposed safety pharmacology studies metabolic profiling.

The budget requested for the full time pharmacologist is $55,000, with 3% increase in each of the subsequent years.

Fringe Benefits

Fringe benefits have been calculated according to the Xavier University guidelines (22% of annual salary and wages for faculty and research associate and 7.65% for student).

Supplies

Funds are requested for purchasing laboratory supplies, including chemical reagents, solvents, analytical standards, HPLC columns and mass spectrometry consumables, and cell culture supplies. The total supplies budget is $35,000 for year 1; $20,076 for year 2; $25,514 for year 3; $24,892 for year 4; $32,211 for year 5.

Travel

Travel for the PI and two research associates to attend conferences on oncology therapeutics. Total travel requested is $4,000 for years 1-2 and $2,250 for years 3 and 4, and $4,000 for year 5.

Other Expenses:

Animals and housing cost

Funds are requested to purchase nude mice ($4,000/y), SCID mice and SD rats ($7,000/y) and for per diem cost ($4,000/y).

Fee for service cost.

These include animal studies that cannot be performed at Xavier's animal facility, including all dog studies and hERG assays, plasma protein binding assays, and CYP inhibition assays.

A total for all animal expenses is $50,000 for years 1; $36,155 for year 2, $31,207 for year 3; $27,668 for year 4; $32,211 for year 5.

Indirect Costs:

Program Director/Principal Investigator (Last, First, Middle): Wang, Guangdi

Indirect cost is calculated based on DHHS Agreement effective 7/1/14. The current Facilities & Administrative cost for Xavier University is 65.5% of the salary and wages base.

RESEARCH & RELATED BUDGET - Cumulative Budget

	Totals ($)	
Section A, Senior/Key Person		190,250.00
Section B, Other Personnel		712,486.00
Total Number Other Personnel	10	
Total Salary, Wages and Fringe Benefits (A+B)		902,736.00
Section C, Equipment		
Section D, Travel		16,500.00
1. Domestic	16,500.00	
2. Foreign		
Section E, Participant/Trainee Support Costs		
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other		
6. Number of Participants/Trainees		
Section F, Other Direct Costs		266,707.00
1. Materials and Supplies	89,466.00	
2. Publication Costs		
3. Consultant Services		
4. ADP/Computer Services		
5. Subawards/Consortium/Contractual Costs		
6. Equipment or Facility Rental/User Fees		
7. Alterations and Renovations		
8. Other 1	177,241.00	
9. Other 2		
10. Other 3		
Section G, Direct Costs (A thru F)		1,185,943.00
Section H, Indirect Costs		508,100.00
Section I, Total Direct and Indirect Costs (G + H)		1,694,043.00
Section J, Fee		

Funding Opportunity Number: RFA-MD-17-006. Received Date: 2017-12-15T12:15:48.000-05:00

PHS 398 Cover Page Supplement

OMB Number: 0925-0001

Expiration Date: 10/31/2018

1. Human Subjects Section

Clinical Trial? ○ Yes ○ No

*Agency-Defined Phase III Clinical Trial? ○ Yes ○ No

2. Vertebrate Animals Section

Are vertebrate animals euthanized? ● Yes ○ No

If "Yes" to euthanasia

Is the method consistent with American Veterinary Medical Association (AVMA) guidelines?

● Yes ○ No

If "No" to AVMA guidelines, describe method and proved scientific justification

3. *Program Income Section

*Is program income anticipated during the periods for which the grant support is requested?

○ Yes ● No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

*Budget Period	*Anticipated Amount ($)	*Source(s)

Funding Opportunity Number: RFA-MD-17-006 . Received Date: 2017-12-15T12:15:48.000-05:00

PHS 398 Cover Page Supplement

4. Human Embryonic Stem Cells Section

*Does the proposed project involve human embryonic stem cells? ○ Yes ● No

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://grants.nih.gov/stem_cells/registry/current.htm. Or, if a specific stem cell line cannot be referenced at this time, please check the box indicating that one from the registry will be used:

Specific stem cell line cannot be referenced at this time. One from the registry will be used.

Cell Line(s) (Example: 0004):

5. Inventions and Patents Section (RENEWAL)

*Inventions and Patents: ○ Yes ○ No

If the answer is "Yes" then please answer the following:

*Previously Reported: ○ Yes ○ No

6. Change of Investigator / Change of Institution Section

❑ Change of Project Director / Principal Investigator

Name of former Project Director / Principal Investigator

Prefix:

*First Name:

Middle Name:

*Last Name:

Suffix:

❑ Change of Grantee Institution

*Name of former institution:

PHS 398 Research Plan

OMB Number: 0925-0001
Expiration Date: 10/31/2018

Introduction	
1. Introduction to Application (Resubmission and Revision)	
Research Plan Section	
2. Specific Aims	wang_specific_aims1001356409.pdf
3. Research Strategy*	Research_Strategy_Project_2__Wang__final1001356356.pdf
4. Progress Report Publication List	Publication_list_reported1001356462.pdf
Human Subjects Section	
5. Protection of Human Subjects	
6. Data Safety Monitoring Plan	
7. Inclusion of Women and Minorities	
8. Inclusion of Children	
Other Research Plan Section	
9. Vertebrate Animals	Animal_protocol_final1001356358.pdf
10. Select Agent Research	
11. Multiple PD/PI Leadership Plan	
12. Consortium/Contractual Arrangements	
13. Letters of Support	
14. Resource Sharing Plan(s)	Resource_Sharing_Plan1001356359.pdf
15. Authentication of Key Biological and/or Chemical Resources	Authentication_of_Key_Biological_andor_Chemical_Resources1001356360.pdf
Appendix	
16. Appendix	

Funding Opportunity Number: RFA-MD-17-006. Received Date: 2017-12-15T12:15:48.000-05:00

Developing an Orally Bioavailable SERD for Treatment of Metastatic/Advanced Breast Cancer

A. SPECIFIC AIMS

In the United States, African American (AA) women are more likely to die from breast cancer than women from any other ethnic groups. The gap in breast cancer mortality between Black and White women has increased from 30.3% in 2000 to 41.8% in 2010 [1-8]. In patients with hormone receptor-positive, HER2-negative disease, AA women were associated with worse disease-free survival [9]. Fulvestrant is the only FDA approved selective estrogen receptor downregulator (SERD) indicated for ER+ metastatic breast cancer as first line endocrine therapy [10,11] and as second line treatment for progressing disease after tamoxifen or aromatase inhibitors (AIs) therapy [12,13]. However, this injection only drug is poorly bioavailable and takes 30 days to reach its maximal steady-state plasma concentration, limiting the clinical response rate to lower than 20% [14]. An oral SERD with greater drug exposure and faster action would bring immediate clinical benefits to patients with advanced breast cancer that have a poorer prognosis. Further, in light of the recent FDA approval of fulvestrant as a combination therapy with CDK4/6 inhibitor palbociclib for advanced breast cancer [15], the clinical utility of an oral SERD in the combination treatment setting will become more significant. So far, advances in oral SERDs development have confined to nonsteroidal molecules, and clinical trials of oral SERDs have yet to move beyond phase 1 safety studies [16,17].

Our lead oral steroidal SERD, ZB716, has shown promising results in preclinical pharmacology, bioavailability, and efficacy evaluations in ER+ breast cancer models [18-20, and Preliminary Studies]. ZB716 binds to ER with high affinity and exerts its antiestrogenic effect on ER+ breast cancer cells. In both tamoxifen naive and resistant breast cancer models, ZB716 potently inhibits cell proliferation and effectively degrades the hormone receptor in a dose-dependent manner. In animals, ZB716 has far superior oral bioavailability and greater efficacy compared to fulvestrant [18-20]. Moreover, in direct comparison to oral SERDs under clinical trials, ZB716 is a stronger antiestrogen and ER-degrader (Preliminary Studies). To further advance the preclinical development of ZB716 we propose to investigate the in vivo efficacy of ZB716, alone and in combination with a CDK4/6 inhibitor, palbociclib in endocrine resistant, patient derived breast tumor models from both White and Black donors. We propose to determine optimal reaction conditions under which ZB716 can be prepared in larger scale, investigate its physical properties and formulation options for toxicological studies in animals, and conduct metabolic profiling, pharmacokinetics, and bioavailability studies.

Specific Aim 1. Conduct pharmacological and mechanistic studies of ZB716, a steroidal oral SERD

Aim 1a: Conduct dose-finding efficacy studies in patient derived xenograft (PDX) breast tumor models. These studies will determine the in vivo efficacy of ZB716 in endocrine resistant breast cancer and identify optimal therapeutically effective oral dose in clinically relevant breast tumor models.

Aim 1b: Determine the synergistic efficacy and optimal dosage of ZB716 in combination therapy with palbociclib (CDK4/6 inhibitor).

Aim 1c. Conduct mechanistic studies on the SERD activity of ZB716 by investigating its modulation of ERα-coregulator interactions and its binding behavior to the mutant estrogen receptor.

Specific Aim 2. Determine optimal reaction conditions, physical properties, and formulation prototypes

Aim 2a. Investigate reaction conditions for each of the four synthetic steps to define phase appropriate optimal routes, identify most efficient and high yielding conditions for scale up preparation of 100 g of ZB716 for all non-GLP pharmacology, stability, and toxicology studies.

Aim 2b. Determine physical properties including solubility at pH 7.4, plasma protein binding, and caco-2 permeability of ZB716.

Aim 2c. Conduct pre-formulation studies to determine an optimal liquid formulation prototype for animal toxicology studies.

Specific Aim 3. Determine safety pharmacology, metabolism, pharmacokinetics, and bioavailability

Aim 3a. Perform safety pharmacology studies including P450 enzyme inhibition studies to determine inhibitory activities towards a panel of P450 enzymes, and hERG assays to assess potential cardiotoxicity.

Aim 3b. Investigate the liver microsomal metabolic profile of ZB716 and determine the excretion pattern of ZB716 after oral administration to mice and rats at various time intervals.

Aim 3c. Determine the absolute ZB716 oral bioavailability by conducting single dose pharmacokinetics with i.v. arm in rats and dogs and repeated dose pharmacokinetics in rats and dogs.

Accomplishing the proposed aims will provide definitive evidence to determine if ZB716 is a safe and more efficacious oral SERD than the currently approved regimen that warrants clinical trials for metastatic/advanced breast cancer that disproportionately impact AA women.

B. RESEARCH STRATEGY

B1. SIGNIFICANCE

Selective estrogen receptor downregulators (SERDs) are a class of endocrine therapy agents that act both as estrogen receptor (ER) antagonists and ER degraders that are effective in treating metastatic or advanced breast cancer. Currently the only FDA approved SERD is fulvestrant, originally indicated for breast cancer progressing after tamoxifen or aromatase inhibitor (AI) treatment [12,13], but recently approved for first line endocrine therapy alone and in combination with palbociclib, a CDK4/6 inhibitor [10,11,15] for postmenopausal patients. While fulvestrant has proven clinically effective with manageable adverse side effects, the drug is well known for its poor bioavailability [14]. It can only be administered as a monthly intramuscular (*i.m.*) injection and has limited drug exposure, insufficient ER turn-over, and lower than 20% objective clinical response rate in patients [14, 21-24]. In the second line or greater setting, the low bioavailability of fulvestrant and its slow action may in particular contribute to limited efficacy because the endocrine-resistant tumor requires an even higher drug exposure [21-24]. In the first line setting, fulvestrant's *i.m.* route and long time to steady state drug concentration in systemic circulation will limit its wider clinical application. Orally bioavailable SERDs with much greater drug exposure and more rapid therapeutic action are highly desirable with potential to bring substantial clinical benefits to patients in need of endocrine therapy, especially in the advanced or metastatic setting.

Advances in oral SERDs development have been confined to **nonsteroidal** molecules among which the most promising SERDs are those containing a cinnamic acid moiety, believed to be a critical structural feature conferring SERD-like properties [24]. Several oral SERDs have entered clinical trials since 2014, including GDC-0810 and AZD9496 [16,17,29]. These compounds showed antiestrogenic activity, ER downregulating efficacy comparable to fulvestrant, and favorable pharmacokinetic profiles in animal models. Their clinical performance, however, has yet to be proven. Indeed, in April 2017, development of GDC-0810 (brilanestrant) was discontinued by Roche due to gastrointestinal toxicities [31-32]. In contrast, steroidal SERDs like fulvestrant are not known for such toxicities. A total of 4 reports [33-36] have described attempts to develop orally bioavailable **steroidal** SERDs. However, no pharmacokinetic data are available and no further progress on pre-clinical studies has been reported since 2010. Indeed, these attempts focused on modifications made primarily to the long alkyl chain to increase polarity and solubility but failed to address the main problem that is responsible for the poor bioavailability of fulvestrant, that is, fulvestrant undergoes rapid and extensive O-glucuronidation [37,38] and O-sulfation [39,40] to form polar metabolites that are inactivated and undergo rapid systemic clearance.

ZB716 minimizes the metabolic inactivation and clearance that prevents fulvestrant from accessing target tissues. We have previously succeeded in significantly reducing first pass metabolism of hydroxylated drug molecules using boronic acid derivatives and enhancing their systemic bioavailability [41,42]. Preclinical studies confirmed that ZB716 retains full binding affinity of the steroidal moiety of fulvestrant while minimizing glucuronidation and sulfation [18-20, and Preliminary Studies]. We found that ZB716 binds to ER with high affinity and exerts its antiestrogenic effect on ER-expressing breast cancer cells. In both tamoxifen naive and tamoxifen resistant breast cancer cells, ZB716 potently inhibits cell proliferation and effectively degrades the hormone receptor in a dose-dependent manner. In mice, we have shown that ZB716 has far superior oral bioavailability when compared to fulvestrant [18,20], and in two ER+ breast cancer xenograft models, ZB716 has proven to be a more efficacious SERD than fulvestrant in inhibiting tumor growth [Prelim. Studies].

With fulvestrant, the 500 mg dose has reached the injectionable limit that can be locally tolerated, but fails to attain the maximum therapeutic effect [15]. ZB716 can deliver a significantly higher systemic drug exposure to increase therapeutic efficacy in a much shorter treatment window, thereby preventing early recurrence and achieving more favorable treatment outcomes than the current SERD regimen. The high oral bioavailability of ZB716 will allow clinical studies to optimize pharmacodynamics to find the dose range where maximal efficacy can be achieved with tolerable adverse effects as both a monotherapy and a combination agent.

B2. INNOVATION

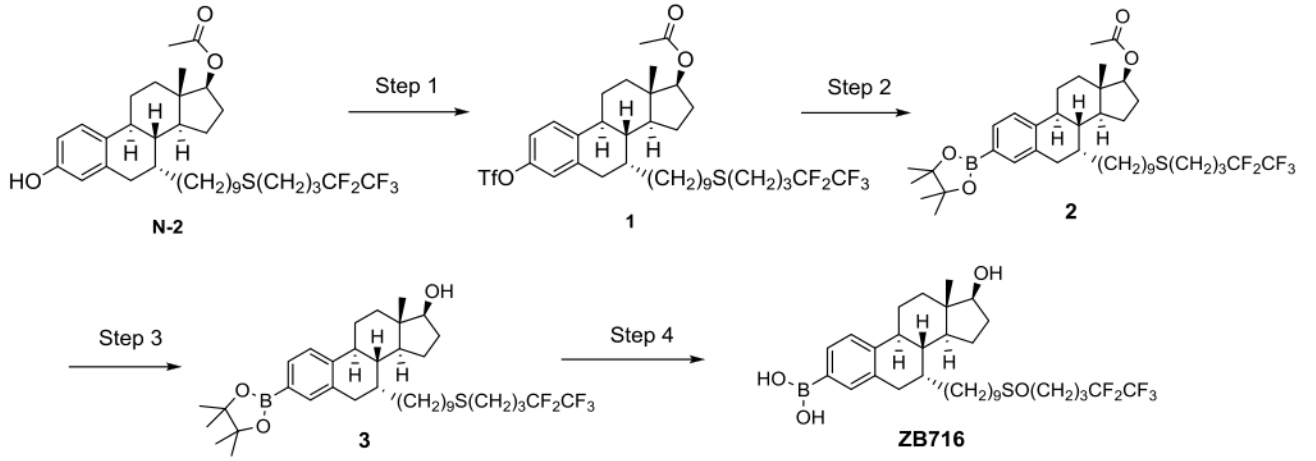
ZB716, a boronic steroidal SERD, represents a novel approach to achieving high oral bioavailability and greater efficacy [18-20]. The specific novelty of this approach is embodied in its remarkable ability to bypass first-pass metabolism while retaining full SERD pharmacology, and its ultimate increase of systemic drug exposure by over 10-fold, all achieved by a novel structural modification. The oral route will greatly shorten the time to steady-state drug concentration of ZB716 from one month to 5-7 days, afford a significantly higher peak plasma concentration than the current ~20 ng/mL level achieved by the 500 mg injection regimen. This critical advantage of ZB716 over fulvestrant in higher oral bioavailability will enable the optimization of oral dosage to minimize adverse side effect while achieving high ER turnover and greater clinical benefits. If successful in advancing to clinical trials, it could be the **first oral steroidal** SERD to be tested in patients.

B3. APPROACH

Preliminary Studies

1. Chemistry

Using a 4-step synthetic scheme, we were able to obtain ~500 mg/batch of 98% pure ZB716 in a powder form. The structure, as shown below in Scheme 1, has been thoroughly characterized by FTIR, NMR, and mass spectrometry. Purity was >98% as determined by HPLC with both a UV detector and a triple quadrupole tandem mass spectrometer detector [18]. The method of preparation and use of ZB716 as an orally bioavailable SERD has been claimed in a recently filed patent (July 1, 2015, WO2016004166A1).



Scheme 1. Synthetic scheme for preparation of ZB716 from the commercially available reagent ((7a,17b)-7-[9-[(4,4,5,5,5-Pentafluoropentyl)thio]nonyl]-estra-1,3,5(10)-triene-3,17-diol 17-acetate (**N-2**). (Step 1) Triflic anhydride, pyridine in DCM, -10 °C; (Step 2) bis(pinacolato)diboron, Pd(dppf)Cl_2, KOAc in 1,4-dioxane, reflux; (Step 3) KOH in CH_3OH and THF at 0 °C; (Step 4) $NaIO_4$, 1N HCl, THF/H_2O (4:1).

2. In vitro pharmacology of ZB716

ZB716 is a potent antiestrogen in breast cancer cells

To determine if ZB716 acts as an antiestrogen, we used the T47D-kb-Luc stably transfected human breast cancer cell reporter gene assay [43] by measuring its ability to inhibit the transcriptional activity of estradiol (E2). Data were normalized relative to the activity of E2 control. The T47D-kb-Luc cells are stably transfected with an artificial gene from the firefly that is only induced if estrogens bind and activate the ER to induce the gene product (Luciferase). As shown in Fig 1, ZB716 inhibits E2-induced ERE reporteractivity in a dose-dependent manner, completely blocking ERE activity at 1 nM.

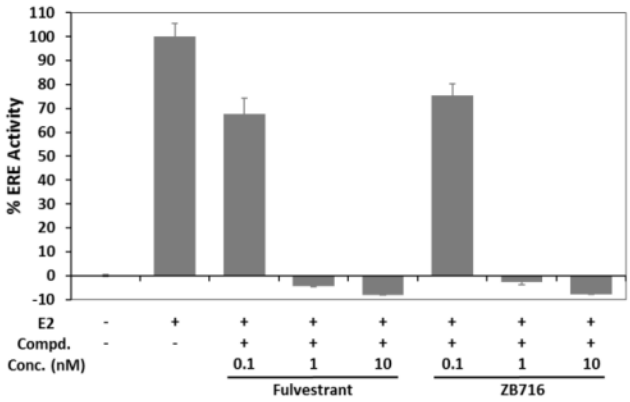


Fig 1. Antiestrogenic effects of ZB716 on T47D-kb-luc cells

ZB716 is effective in inhibiting breast cancer cells overexpressing Y537S mutant ER

To determine if ZB716 is an effective SERD in breast cancer cells that are ligand-independent, we used an ESR1 mutant cell line, T47D/Y537S that was derived from a PDX model [44] as an endocrine resistant cell line. Cells were treated with ZB716 or fulvestrant at concentrations ranging from 0.1 nM to 1 μM, and demonstrated a dose-dependent inhibition of growth; the IC_{50} for ZB716 and fulvestrant was found at 2.44E-08 M and 3.20E-08 M, respectively, about 10 times higher than in the T47D cells with wild type ER [6]

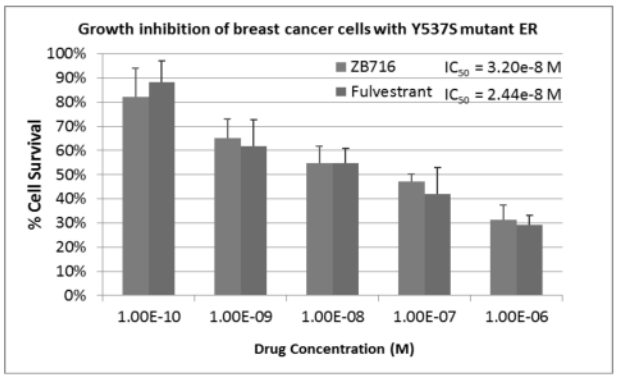


Fig 2. T47D-Y537S cell inhibition by ZB716 or fulvestrant.

ZB716 is more effective than nonsteroidal oral SERDs in blocking tamoxifen-resistant breast cancer cell growth. To test the potency of ZB716 against hormone resistant breast cancer cells we determined its IC_{50} values in MCF-7, T47D, and their tamoxifen resistant variants, MCF-7/TamR and T47D/PKCα. MCF-7/TamR has been maintained in our lab by prolonged treatment of MCF-7 with 4-hydroxytamoxifen (4-OHT) [45], and T47D/ PKCα cells were characterized previously [46-47]. Cells were treated with vehicle or 6 different

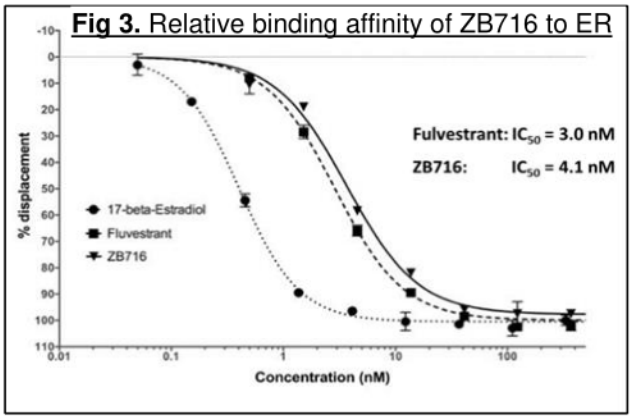
concentrations, ranging from 10^{-10} to 10^{-5} M of ZB716, fulvestrant, GDC-0810, or AZD9496 for 3 days before counting of survived cells. Results in **Table 1** demonstrate that ZB716 behaves as a strong antiestrogen with potency comparable to fulvestrant but greater than GDC-0810 and AZD9496 in both MCF-7 and T47D cells. ZB716 is active against tamoxifen resistant MCF-7 and T47D variants, with IC_{50} values similar to fulvestrant, but significantly lower than the two non-steroidal oral SERDs currently in clinical trials.

Table 1. ZB716 inhibits ER+ breast cancer cells

IC_{50} (μM)	Fulvestrant	ZB716	GDC810	AZD9496
MCF-7	0.0034	0.0016	0.0115	0.0048
T47D	0.0012	0.0061	0.0204	0.0076
MCF7/TamR	0.0228	0.0693	0.1337	0.0928
T47D/PKCα	0.0420	0.0370	0.0809	0.0791

ZB716 binds to ER with high affinity (IC_{50}=4.1nM, Fig 3). To determine the binding affinity of ZB716 to ER, the LanthaScreen TR-FRET assay (Life Technologies) was used in which ZB716 competes with a fluomone ligand and the percent displacement was quantitatively correlated to the fluorescence intensity from the displaced tracer. **Fig 3** shows the competitive binding curves of ZB716 and fulvestrant, with IC_{50} values measured at 4.1 nM and 3.0 nM, respectively.

Fig 3. Relative binding affinity of ZB716 to ER



In-silico modeling confirms ZB716 binds to ER in a similar way as fulvestrant

We compared the binding of ZB716 and fulvestrant to ER_{α} in the antagonistic conformation using a molecular docking method. Our study shows (**Fig 4**) that both fulvestrant and ZB716 can bind to the antagonistic ligand binding site of ERα with high compatibility. The steroidal moiety of the fulvestrant molecule (Fig 4A) binds exactly in the same region as the main scaffold of the antagonistic ligands, which is almost identical to the binding of estradiol to ERα [38]. ZB716 (Fig 4B) binds to ERα in a similar manner as the fulvestrant. The 3-OH of the fulvestrant formed hydrogen bonds with Glu353 and Arg394 [48-51]. In ZB716, 3-OH was replaced with a boronic acid group, yet the placement of the estradiol moiety of ZB716 in the binding pocket and hydrogen bond formation with Glu353 and Arg394 were conserved. This was achieved because of the smaller size of boron, and it required only a slight (0.7Å) shifting of the molecule along the binding pocket as seen in the superimposed structures of Fulvestrant and ZB716 (Fig 4C).

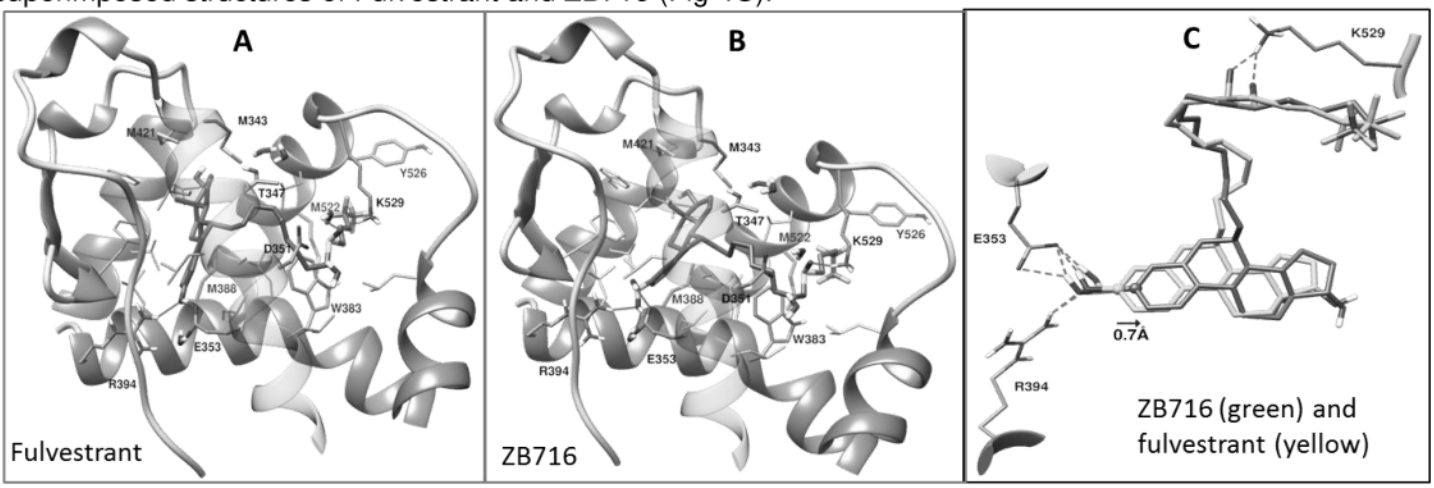


Fig 4. Binding postures of ZB716 and fulvestrant in the antagonistic binding site of ERα.Important amino acids in the binding pockets are shown in stick models, among them the hydrophobic residues are shown in grey, and ERα is depicted in ribbon model. Both Fulvestrant and ZB716 form hydrogen bond with Glu353, Arg394 and Lys529. (A) Fulvestrant in complex with ERα, (B) ZB716 in complex with ERα, (C) superposition of Fulvestrant and ZB716 in ERα binding pocket.

ZB716 downregulates ER in hormone-sensitive, hormone-resistant, and ER mutant breast cancer cells

Hormone-sensitive and resistant breast cancer cells. We next determined ZB716's ability to degrade ER as compared to fulvestrant. ER+ MCF-7 cells were treated with increasing concentrations of ZB716 or fulvestrant. IC50 of ZB716 was 0. 8 nM vs. 0.6 nM of fulvestrant. These results confirm that ZB716 is as potent as fulvestrant in its action as a SERD (Fig 5A). Moreover, in direct comparison to the two nonsteroidal oral

SERDs, ZB716 is more effective in downregulating ER in T47D/PKCα breast cancer cells (Fig 5B) with its IC50 at 4.7 nM, compared to 9.8 nM for AZD9496 and 95 nM for GDC-810.

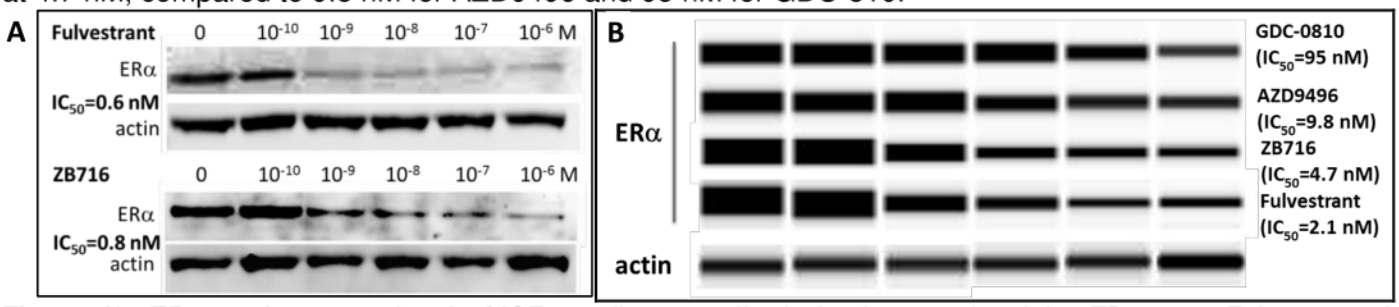


Fig 5. A). ER protein expression in MCF-7 cells was effectively downregulated by ZB716 or Fulvestrant dose-dependently. B). Dose-dependent downregulation of ER in T47D/PKCα cells by ZB716, fulvestrant, GDC-0810, or AZD9496 using a Protein-Simple Wes capillary western blot system. Automated electrophoresis and immunodetection were performed in the WES capillary system. Protein peak areas from electropherograms were converted to virtual images as shown

ZB716 is effective in degrading ER in breast cancer cells harboring ESR1 mutant (Y537S)

The ability of ZB716 to downregulate a constitutively active mutant ER (Y537S) which is resistant to both antiestrogens and aromatase inhibitors, was also evaluated by a WES analysis system (**Fig 6**). This is a clinically more relevant endocrine resistance model in that *ESR1* mutations are found in recurring advanced breast cancer at high frequency [44, 52-56]. When breast cancer cells harboring mutant ER (Y537S) were treated with either ZB716 or fulvestrant, downregulation of ER by 50% required approximately 10 times higher drug concentration, as reflected in the IC_{50} values, which are 24 nM for ZB716 and 11 nM for fulvestrant. This finding suggests that, to be therapeutically effective in vivo, a SERD is required to afford at least 10-fold higher drug exposure to tumor sites.

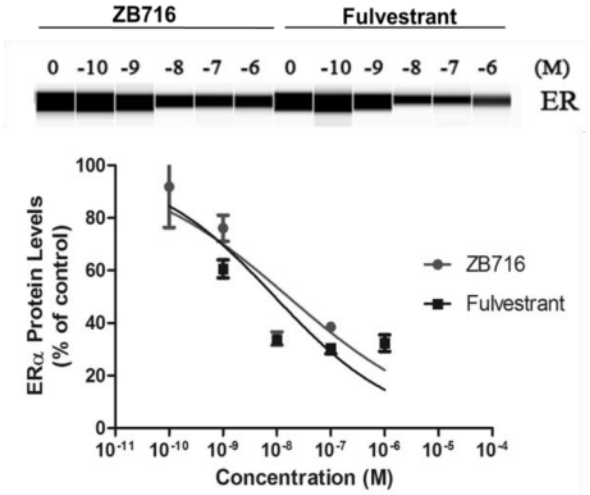


Fig 6. Dose-dependent ER downregulation in ESR 1(Y537S) breast cancer cells by ZB716

3. Pharmacokinetic study of ZB716 in mice, rats, and dogs

Single dose PK in mice, rats, and dogs. To verify if oral administration of ZB716 can achieve a therapeutically effective drug concentration that is systemically available, we conducted pharmacokinetic studies of ZB716 in mice, rats, and dogs. After a single oral dose of ZB716, blood samples were collected from the animals and resulting plasma were analyzed for concentration of ZB716 at various time points after drug administration. Shown in **Figs 7** are plasma total drug concentrations achieved after oral administration of the drug in three different species of animal models. ZB716 afforded over 160 ng/mL peak concentration, a level that far exceeds the plasma drug concentration achieved by fulvestrant when given by s.c. injection to mice (peak concentration of fulvestrant was 14 ng/mL, ref 18), providing definitive evidence that oral bioavailability of ZB716 is superior.

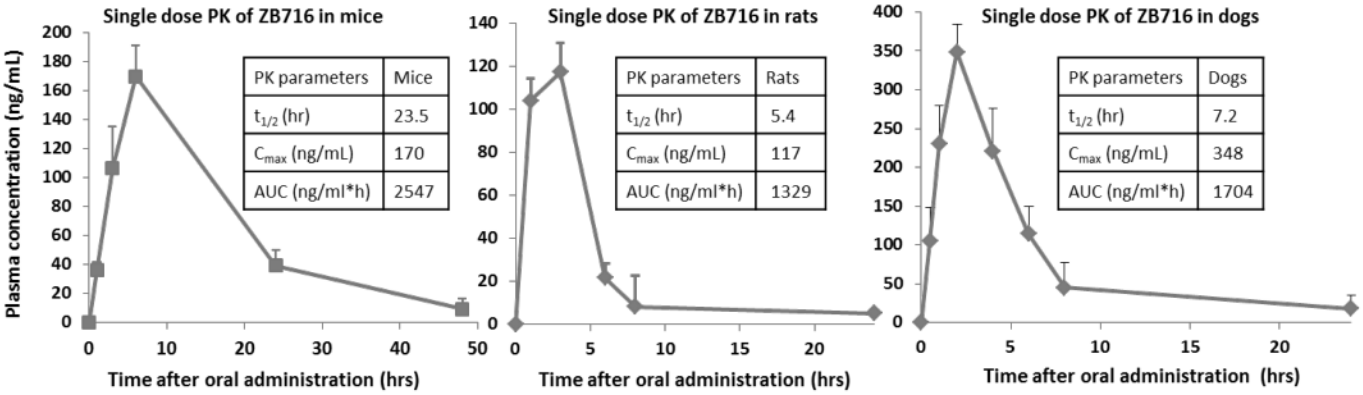


Fig 7. Single dose pharmacokinetics in mice, rats, and dogs after administration of 5 mg/kg ZB716 PO.

4. In vivo Pharmacology

ZB716 is more effective than fulvestrant in blocking growth of breast cancer xenograft in mice

To test the efficacy of orally administered ZB716 in vivo, we used an MCF-7 human breast cancer xenograft model in nude mice. Upon on tumor formation, the animals were randomized into four groups, and treated with vehicle, fulvestrant at 200 mg/kg weekly by subcutaneous injection, or ZB716 at 10 mg/kg or 30 mg/kg by oral gavage. As shown in **Fig. 8**, treatment with ZB716 resulted in complete blockage of tumor growth at both 10 mg/kg and 30 mg/kg, indicating that the lower dosage may have reached full therapeutic efficacy. Moreover, analysis of active drug concentration in final plasma collected from mice at end of study confirmed that final plasma concentration of total active ingredients was over 6 times higher in the 10 mg/kg treatment group, and nearly 30-fold higher in the 30 mg/kg treatment than that in the fulvestrant treated mice, reflective of a steady-state level that primarily accounts for the superior efficacy of ZB716 as compared to fulvestrant treatment.

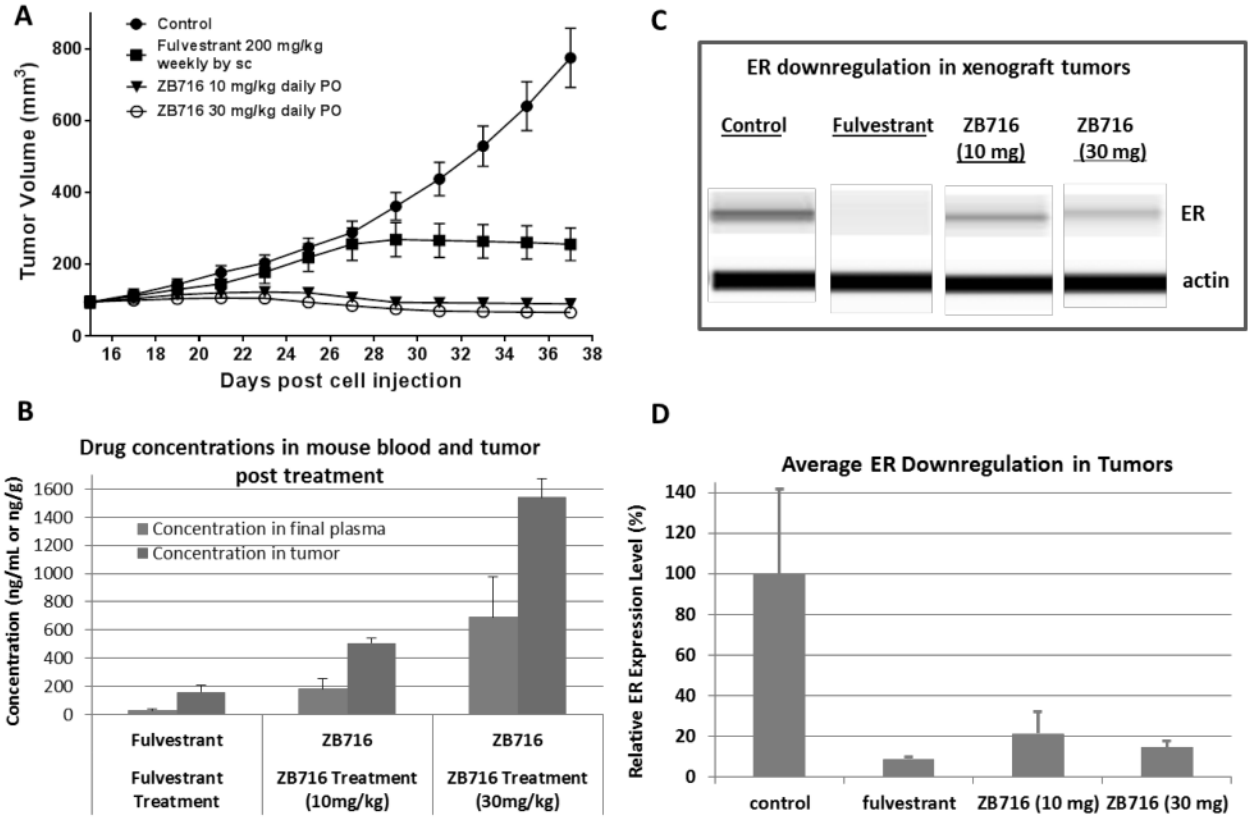


Fig 8. Nude mice bearing MCF-7 breast cancer xenograft were treated with either fulvestrant by s.c. injection or two different oral doses of ZB716. Treatment continued for three weeks before the animals were sacrificed and plasma and tumor tissues were collected. A. tumor volumes were plotted vs. days of treatment; B. concentration of ZB716 and fulvestrant in final plasma and tumor tissue samples at end of study; C. WES analysis of ER expression in tumors collected at end of study; and D. average ER downregulation in tumor tissues at end of study

ZB716 effectively blocks growth of a patient derived xenograft of ER+ primary breast tumor

The efficacy of orally administered ZB716 was next evaluated in a patient-derived xenograft mouse model in which the primary tumor donated by a postmenopausal patient was engrafted in NOD *scid* gamma (NSG™) mice Redacted by agreement This model has been immunohistochemically confirmed as ER+/PR+/ HER2- invasive ductal carcinoma. PDX tumor bearing mice were treated with vehicle, fulvestrant by s.c. injection, ZB716 at 5mg/kg PO, or ZB716 at 20 mg/kg PO. As shown in **Fig. 9**, ZB716 at both doses were effective in blocking tumor growth in the PDX mice, with the 20 mg/kg treatment group showing the greatest effect on growth inhibition.

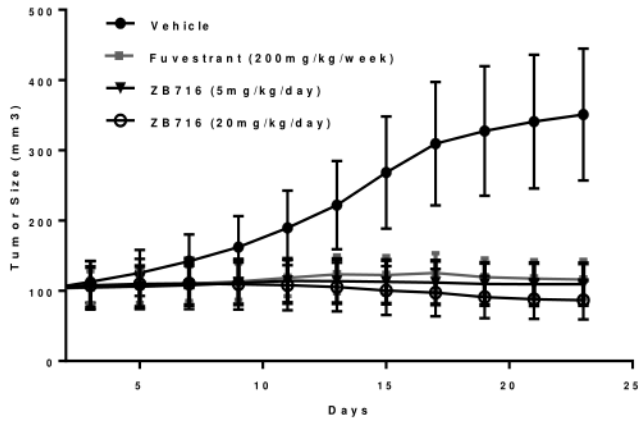


Fig 9. Inhibition of PDX breast tumor growth by ZB716 orally administered to mice at 5 and 20 mg/kg daily, compared to fulvestrant subcutaneously injected at 200 mg/kg weekly.

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RESEARCH DESIGN

The main objective of this application is to investigate the in vivo efficacy of ZB716 in ESR1 mutant, endocrine resistant, as well as primary, estrogen dependent, metastatic PDX breast tumor models that most closely resemble clinical settings for which SERD is currently indicated (first line and second line). We will also determine optimal reaction conditions, physical properties, and formulation prototypes for ZB716, and conduct studies to determine its safety pharmacology, metabolism, pharmacokinetics, and bioavailability, all of which will provide crucial data required to move forward with subsequent clinical development. Additional objectives include the preclinical evaluation of a combination of ZB716 with a CDK4/6 inhibitor, palbociclib and mechanistic investigations of the activity of ZB716 on patient-derived xenografts (PDX) expressing mutant forms of ESR1 (the gene encoding ERα).

Specific Aim 1. Conduct pharmacological and mechanistic studies of ZB716 as a steroidal oral SERD

Aim 1a: Conduct dose-finding efficacy studies in patient derived xenograft (PDX) breast tumor models

Conduct dose-finding efficacy experiments in patient derived breast tumor xenograft models to determine ZB716 efficacy and identify optimal therapeutically effective oral dose. Highly characterized ER+ PDX models will be obtained from Washington University. Xavier University has signed an MTA with Washington University's HAMLET Core to acquire the WHIM tumor lines. We plan to study the efficacy of ZB716 in five models representative of Luminal A and Luminal B subtypes, primary and metastatic tumor sites. All the models have been subjected to whole genome sequencing and whole transcriptome RNA-Seq [44, 54]. Three are from Caucasian patients and two from African-American patients. One is estrogen-dependent, four are estrogen-independent, and two carry different ESR1 mutations (**Table2**). WHIM11 is E2-independent, representing patients unlikely to benefit from SERM/AI treatment but can be potentially treated with SERD as a first line endocrine therapy. WHIM26 represents an advanced metastatic yet E2-dependent setting to test ZB716 efficacy compared to SERM/AI treatment. WHIM9 retains wild type ER but is a recurring E2 independent phenotype for which SERD may be the only option as endocrine therapy. Both WHIM20 and WHIM18 are progressed diseases with ER mutants and thus E2 independent for which SERD efficacy is crucial.

Table 2: PDX model characteristics

PDX model	Subtype (PAM50)	Donor race	ESR1 genotype	E2-dependent	Site of biopsy
WHIM26	Luminal A	White	WT	Yes	Node metastasis
WHIM11	Luminal B	White	WT	No	Primary
WHIM9	Luminal B	AA	WT	No	Skin metastasis
WHIM20	Luminal A	White	Y537S	No	Skin metastasis
WHIM18	Luminal B	AA	YAP1	No	Skin metastasis

In the first set of experiments (Table 3), we will identify the optimal doses of ZB716 in each model. Low-passage xenografts will be implanted into ovariectomized, 5-week old NSG mice. WHIM26-implanted mice will receive estrogen as estradiol pellets. Once tumors will reach approximately 200mm^3, mice will be randomized to treatment arms and treated for 4 weeks or until humane endpoints are reached. If complete tumor regression is observed, animals will be taken off treatment and monitored for recurrence for 4 additional weeks. Tumor volume will be measured every three days. Animals will be weighed daily and monitored for signs of toxicity (weight loss, behavioral changes).

The primary experimental endpoint measured in PDX experiments will be tumor volume change from baseline at the end of treatment (ANOVA with Bonferroni correction for multiple comparisons and alpha = 0.05); this was chosen to mimic a clinical setting whereby patients are evaluated radiologically for response rates at specified intervals. Dose-response curves will be constructed, and subsequent experiments will be performed at the minimal effective dose for each model.

Table 3: PDX Treatment arms, dose finding experiment

Treatment Arm	Vehicle	Fulvestrant	ZB716
Control	+	-	-
Fulvestrant	-	5 mg/week sc	-
ZB716 – Dose level 1	-	-	5 mg/kg po qd
ZB716 – Dose level 2	-	-	10 mg/kg po qd
ZB716 – Dose level 3	-	-	30 mg/kg po qd
ZB716 – Dose level 4	-	-	50 mg/kg po qd

Aim 1b: Determine the synergistic efficacy and optimal dosage of ZB716 in combination therapy with palbociclib (CDK4/6 inhibitor). In the second set of experiments, we will study the efficacy of ZB716 in combination with palbociclib (CDK4/6 inhibitor). After showing clinically significant improvement in median progression free survival (PFS) in PALOMA-3 international phase 3 trial, FDA approved palbociclib (Ibrance,

Pfizer) for use in combination with fulvestrant (Faslodex, Astra- Zeneca) for the treatment of women with ER positive, HER2-negative advanced or metastatic breast cancer (MBC) with disease progression following previous endocrine therapy [14]. This latest development represents a significant advance in the treatment of metastatic HR-positive breast cancer which effectively expands the clinical utility of SERDs. We hypothesize that an oral SERD could offer even more pronounced clinical benefits given its greater bioavailability and drug exposure level. As shown in Table 4, the doses of palbociclib were chosen based on the recent literature on non-steroidal SERM preclinical characterization [44]. PDX tumors will be established as described in **Aim 1a**, and animals will be randomized to treatment arms shown in Table 4.

Table 4: Treatment arms for combination experiments

Treatment Arm	Vehicle	Fulvestrant	ZB716	Palbociclib
Control	+	-	-	-
Fulvestrant	-	5 mg/wk sc	-	-
ZB716	-	-	MED* po qd	-
Fulvestrant/palbociclib	-	5 mg/wk sc	-	-
ZB716/palbociclib	-	-	MED* po qd	45 mg/kg po qd

*MED = minimum effective dose

The primary endpoint will be as described for Aim 1a. If sufficient residual tumors remain at the end of treatment, these tumors will be harvested and characterized as follows: 1) IHC for ER, Ki67, cleaved Caspase 3 and CD31; 2) DNA and RNA isolation for whole exome NGS; chromosomal arrays and whole transcriptome RNASeq. The latter experiments will determine whether residual tumors after 4 weeks of treatment have selected clones carrying specific mutations or altered their gene expression profiles compared to control tumors. The whole genome sequences and whole transcriptome gene expression profiles of these models have been extensively characterized [44], and these experiments will be able to assess whether tumors that survive treatment with ZB716 alone or in combination select specific mutations, CNVs or gene expression profiles. If complete tumor regression is observed, we will retain animals for 4 weeks and evaluate recurrence-free survival rates at 4 weeks.

<u>Aim 1c.</u> Conduct mechanistic studies on the SERD activity of ZB716 by studying its modulation of ERα-coregulator interactions and its binding behavior to the mutant estrogen receptor.

ZB716- induced modulation of ERα-coregulator interactions

Molecular modeling shows highly similar ERα-binding modes of fulvestrant and ZB716. This suggests that upon binding to the ligand binding pocket both compounds induce a similar LBD conformation and affinity for coregulator proteins. To test this, we propose to measure binding of ERα LBD to a peptide microarray containing 154 individual (CoR-) NR-boxes of a set of 60+ coregulators in the absence (apo) or presence of ZB716. This study will provide mechanistic insight into the mode of action by ZB716 both as a pure antiestrogen and as an ER downregulator, when compared to fulvestrant as an established steroidal SERD, AZD9496, a nonsteroidal SERD currently under clinical evaluation, and 4-hydroxytamoxifen, a known potent SERM. We will use a Micro Array Assay for Real-time Coregulator Nuclear receptor Interaction (MARCoNI, PamGene, Belgium) under a fee for service agreement with PamGene, the company that provides the platform for the co-regulator assays [57]. Briefly, a reaction mix with ERα LBD and fluorescently labeled detection antibody with 10 μM of ZB716 or solvent (DMSO, 2% final concentration) only is incubated on a microarray containing 154 coregulator-derived NR-binding motifs. Each condition is measured using 3 technical replicates (arrays). After incubation, unbound receptor is removed by washing, and a tiff image of each array is acquired using a CCD camera and receptor binding to each peptide on the array is quantified using dedicated software. For each condition, the three technical replicates are used to calculate mean and S.E.M. ERα binding as well as compound-induced log-fold modulation vs. control for each individual motif. Significance of the modulation is assessed using Student's t-Test. For comparison, known and well-characterized SERDs including the steroidal fulvestrant and nonsteroidal AZD9496 and a SERM (4-hydroxytamoxifen) will be included in the assays.

Binding behavior of ZB716 towards the mutant ER (Y537S)

Our preliminary studies have demonstrated that ZB716 is effective in degrading ER and inhibiting growth of breast cancer cells that express a mutant, ligand-independent ER. In Aim 1a, we proposed to test the efficacy of ZB716 in a panel of PDX models in vivo. It is thus important to ascertain if ZB716 exerts its SERD activities through binding the mutant receptor. To test this, we will first obtain a purified recombinant Estrogen Receptor Alpha (ER alpha) LBD GST protein containing a Y537S mutation. The single point mutation will be prepared based on the Life Technologies ER alpha LBD GST construct (amino acids 282-595, accession Number:

NP_000116.2). The construct will be expressed in insect cells and the protein will be purified using Life Technologies proprietary methods under an agreement signed between Xavier University and Life Technologies in 2016. The final purified protein will be tested in a LanthaScreen® TR-FRET ER Alpha Competitive Binding assay and in a LanthaScreen® TRFRET ER Alpha Coactivator Assay. Competitive binding assays on ZB716 along with the steroidal SERD, fulvestrant, and a nonsteroidal oral SERD, AZD9496.

Specific Aim 2. Determine optimal reaction conditions, physical properties, and formulation prototypes. T

Aim 2a. Investigate reaction conditions for each of the four synthetic steps to define phase appropriate optimal routes, identify most efficient and high yielding conditions for scale up preparation of 100 g of ZB716 for all non-GLP pharmacology, stability, and toxicology studies. We will use the synthetic route developed in our laboratory that is in the hundred miligrams scale as the basis for scale-up to obtain approximately 100 grams of ZB716. This aim will answer the critical question as to whether the current synthetic conditions can be further optimized and reproduced at a larger scale with quality control. Further, this aim will ensure reproducibility and quality control of the synthetic protocols that will be later adapted in the GMP compliant manufacturing of ZB716 API.

Synthetic method optimization for scale up process

Using a modified 4-step reaction scheme as shown in Scheme 1 (Preliminary Studies), we will attempt to scale up the synthesis to 35 g starting material (**N-2**) per batch to obtain 5-7 g crude ZB716 as a fine powder after rotary evaporation. Upon chromatography purification, we seek to obtain 3-5 g of >99% pure ZB716 per batch. The synthesis at this scale will be repeated to ensure reproducibility of quality and yield. These reactions have been used in our laboratory to obtain ZB716 for all preclinical studies conducted up to date and are considered feasible and scalable.

Reaction Improvements on each of the 4 synthetic steps scalable manufacturing:

Step 1:

We will attempt to eliminate the use of pyridine as an environmentally hazardous solvent for this reaction by identifying an alternative solvent and potentially an alternative base. We will also evaluate the potential for a solvent exchange and a telescoped procedure into the next step. In addition, we will test the suitability of Class 3 solvents to replace dichloromethane (DCM) as a solvent in the reaction which is less desirable in larger operations.

Step 2:

We will first perform a catalyst screen to optimize the borylation reaction and test alternative purification methods in order to eliminate the chromatographic purification process. We will next test a panel of Class 3 solvents with the goal of replacing 1,4-dioxane as a solvent in this reaction. Furthermore, we will evaluate an acid/base extraction method for purification of boronate ester **2** for potentially telescoping the intermediate into the next reaction step. Finally, we will evaluate the need for scavenging the residual of palladium from the catalyst use.

Step 3:

The main process improvement endpoint in this reaction step is to develop an alternative workup and purification procedure to replace the original chromatographic purification method for intermediate **3**.

Step 4:

A panel of Class 3 solvents will be screened and evaluated for possible substitution of dichloromethane solvent. We will also test if sodium periodate is the optimal oxidant for this dual-purpose reaction to oxidize the sulfur moiety and to enable cleavage of pinacol boronic ester group. We will focus on the oxidative selectivity to form sulfoxide vs. sulfone and the completeness of conversion from ester to boronic acid. More importantly, as the preferred choice of purification method for the final product, recrystallization conditions will be tested to eliminate chromatographic purification. Measurement of Pd residues will be carried out in the final API product.

Analytical and bioanalytical method optimization and validation

We will validate and standardize chromatography- and spectrometry-based analytical methods for structure and purity analysis of ZB716 as a synthetic product. Bioanalytical methods for determination of ZB716 and its metabolites in plasma samples will also be validated and standardized. The proposed synthetic and analytical work will be conducted at Xavier University's RCMI Cancer Research Center where all needed analytical instrumentation is available.

Aim 2b. Determine physical properties including solubility at pH 7.4, plasma protein binding, and caco-2 permeability.

Solubility in saline (PBS buffer at pH 7.4)

To determine ZB716's solubility in pH7.4 phosphate buffer solution we will use an HPLC quantitation based method. Briefly, a stock solution of 10 mM ZB716 will be prepared (ZB716 is completely soluble in DMSO at this concentration), and an aliquot of 0.2 mL of this stock solution is added to 9.8 mL of aqueous HEPES buffer at pH 7.4, at ambient temp. The resulting solution is incubated at 37 ^{o}C for 24 hours, centrifuged, and sampled for HPLC-UV analysis. We have previously determined that ZB716 exhibits maximum absorbance at 230 nM, which will be used to establish a calibration curve of Peak area vs. ZB716 concentration. The concentration of ZB716 in the final clear solution will be determined by HPLC in μM.

Plasma protein binding

ZB716 has demonstrated excellent pharmacokinetic and pharmacodynamics properties in preclinical animal models. We will characterize its binding behaviors to plasma proteins including albumin, α_1-acid glycoprotein, lipoproteins and α, β, and γ globulins. We will use an equilibrium dialysis method to measure the free and bound ZB716. The assay will be performed in a 96-well Teflon dialysis unit. Each well consists of 2 chambers separated by a vertically aligned dialysis membrane of predetermined pore size of 10 k molecular cutoff. Plasma spiked with ZB716 will be added to 1 chamber and buffer to the other chamber. Incubation will continue for 6 hours during which time free compound is allowed to diffuse from the plasma chamber to the buffer chamber until equilibrium is reached. Samples will be collected at time 0 and 6 hrs from each chamber for quantitative analysis of free ZB716 by UHPLC-MS/MS. The unbound fraction is calculated as the concentration in the buffer side divided by the total concentration in the plasma side.

Caco-2 permeability

Permeability assays using the Caco-2 colon carcinoma cell line are universally used to estimate the ability of potential drug compounds to cross the intestinal epithelium. We will use Caco-2 cell monolayers grown on microporous membranes in multiwell insert systems to determine the permeability of ZB716. With the inserts suspended in the wells of multiwell plates, ZB716 will be added to the upper (apical) chamber to measure permeability in the absorptive (apical to basolateral) direction. Samples are then taken from the opposite chamber at various time intervals to measure the amount of ZB716 that has crossed the cell monolayer. Briefly, Caco-2 cells will be maintained at 37°C in DMEM in a humidified atmosphere of 5% CO_2, and the medium will be changed every two days. Cells will be subcultured at 70-80% confluence by splitting them with trypsin, confluent Caco-2 cells are then subcultured at passage 30-40. Lucifer yellow and TEER (Transepithelial electrical resistance) will be used as indicators for the determination of the monolayer integrity. The monolayer will be rinsed with Hank's balanced salt solution (HBSS) and 200 µL of ZB716 solution with varying strength will be added into the apical chambers of the monolayers inserted in a plate containing 600 µL HBSS. After 2 hours of incubation at 37°C, 50 µL of the solution will be removed from the apical and basolateral wells and analyzed using UHPLC-MS/MS method.

Aim 2c. Conduct pre-formulation studies to determine an optimal liquid formulation prototype for animal toxicology studies.

Pre-formulation studies

Solubility and Characterization of ZB716

In preparation for solid state and formulation studies on ZB716, we will first characterize the free base form of the compound by X-ray powder diffraction (XRPD), polarized light microscopy (PLM), differential scanning calorimetry (DSC), thermogravimetry (TGA), dynamic vapor sorption (DVS), and 1H NMR. The solubility of ZB716 will be measured at ambient temperature in unbuffered water and at pH 1, 3, 5, 7, and 9. Solubility will be tested in triplicate with supernatant from each sample analyzed by HPLC, and the solids pooled for XRPD analysis. In addition, solubility of ZB716 will be measured in 15 different organic solvents of varying polarity at ambient temperature and solids will be collected for XRPD analysis as detailed in the stable form screen work.

Stable Form Screen

In preparing for larger scale manufacturing of ZB716, a stable form screen will be done to ensure the most stable polymorph of the free base is consistently isolated. We will conduct 25-30 experiments using crystallization techniques that promote more stable polymorphs, such as slow cooling, slow evaporation, vapor diffusion, and slurries over an extended period of time, etc. Because a variety of organic solvents and aqueous mixtures will be used, the propensity of ZB716 to form solvates and/or hydrates will be studied within this stable form screen. Crystalline material isolated from experiments will be analyzed by XRPD. If new XRPD

patterns are observed, the material will be further characterized by DSC and TGA. Any new polymorphs discovered during the stable form screen will be scaled up to ~200 mg and subjected to competitive slurries to determine the most thermodynamically stable form, and whether the polymorphs are enantiotropically or monotropically related. Two solvents at two temperatures will be considered for the competitive slurries

Abbreviated Salt Screen

We will conduct a salt screen for ZB716 to find crystalline materials. Briefly, the pKa of the free base will be measured in duplicate using a potentiometric technique. The average pKa will be used to select approximately 8-12 pharmaceutically acceptable acids to use in a screen. Approximately 20-25 salt-forming experiments will be performed and various crystallization techniques will be employed, include cooling, slurrying, solvent/anti-solvent precipitation. If salt formation is confirmed, the sample will be further characterized by DSC, TGA, and DVS to better understand the thermal properties and hygroscopic nature of the salt. We will then select up to three salts for scale-up to ~200 mg scale to allow solubility tests in two media at one temperature (or one media at two temperatures). The three salts selected will also be stored at accelerated conditions and monitored for evidence of deliquescence.

Preclinical formulation prototype development

To enable animal toxicology studies, a liquid formulation prototype will be developed. Approximately 10 – 15 excipients will be selected with a targeted dose based on the GLP toxicity study protocols [58]. The samples will be prepared at that target concentration at ambient temperature. To achieve the target dose, solubilizing agents such as co-solvents, surfactants and cyclodextrins will be considered. To conserve material, initial scouting will be performed at small scale (≤ 1 mL), moving up in scale to ~1-5 mL as top formulations are identified for optimization. It is anticipated that initial scouting will require up to 40 experiments, followed by approximately 10 optimization experiments before conducting stability tests, with the intent of proceeding with the lowest excipient/buffer concentrations that meet the solubility and stability requirements of the drug substance. If a clear solution is obtained, the sample will be monitored for any evidence of precipitation over 1 week. If a clear solution is not obtained, the sample will be stirred for ~24 hours and the supernatant analyzed by HPLC to determine the solubility value. If a solution formulation is not achievable, a suspension formulation will be developed. The pH and appearance will be recorded for each experiment. A single formulation will be selected based on these results and the solution stability of the formulation will be tested at T = 0, 1, and 2 weeks at ambient conditions in glass vials.

Aim 3. Determine safety pharmacology, metabolic profiling, pharmacokinetics, bioavailability studies

Aim 3a. Perform safety pharmacology studies including P450 enzyme inhibition studies to determine inhibitory activities towards a panel of P450 enzymes, and hERG assays to assess potential cardiotoxicity.

CYP450 inhibition

To determine the potential of ZB716 in eliciting pharmacokinetic drug interactions via inhibition of cytochrome P450 activities, we propose to conduct CYP inhibition assays of ZB716 effect on seven P450 enzymes: CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Serial dilutions of ZB716 stock solution (test concentrations of 0.01 to 10 μM) will be prepared in a 9:1 solution of DMSO for CYP450 inhibition testing. The final DMSO content in the reaction mixture will be equal in all solutions used within an assay and will be less than 0.2%. ZB716 will be incubated at 7 increasing concentrations in duplicate with human liver microsomes in the presence of 2 mM NADP (NADPH) in 100 mM potassium phosphate (pH 7.4) containing 5 mM magnesium chloride and a probe substrate, in a 200 μL assay final volume. The probe substrates will be phenacetin (CYP1A2), bupropion (CYP2B6), amodiaquine (CYP2C8), diclofenac (CYP2C9), (S)-mephenytoin (CYP2C19), dextromethorphan (CYP2D6), chlorzoxazone (CYP2E1), felodipine (CYP3A4). These validated selective CYP inhibitors [59] will be screened alongside ZB716 as a positive control. After incubation for 5 min at 37°C, the reactions will be terminated by addition of methanol-containing internal standard (propranolol) for analytical quantification. The quenched samples will be incubated at 4°C for 10 min and centrifuged at 4°C for 10 min. The supernatant will be removed, and the probe substrate metabolite will be analyzed by LC-MS/MS. A decrease in the formation of the metabolite compared to vehicle control will be used to calculate a 50% inhibitory concentration (IC_{50} [the test concentration that produces 50% inhibition]).

hERG (I_{Kr}) Assay

The ICH S7B guideline recommends a general non-clinical testing strategy for determining the propensity of non-cardiovascular drugs to delay ventricular repolarization, an effect that may progress to life-threatening ventricular arrhythmia. A lengthened QT interval (a measure of the time between the start of the Q wave and

the end of the T wave in the heart's electrical cycle) is a marker for the potential of ventricular tachyarrhythmias like torsades de pointes (TdP) and a risk factor for sudden death. As a key part of safety pharmacology assessment, we will conduct hERG inhibition assay to evaluate the potential cardiovascular risk of ZB716.

The hERG potassium channels will be stably expressed in the Chinese hamster ovary (CHO)-K1 cells. The CHO-K1 cells are maintained in cell media that contain 90% Iscove's modified Dulbecco's medium, 10% fetal bovine serum, 1% HT supplement, 1% non-essential amino acid (NEAA), penicillin G sodium 100 U/mL, streptomycin sulfate 100 mg/mL and geneticin 500 mg/mL. Confluent cells in flasks were rinsed once with PBS prior to passage. The flasks will be incubated with Versene (EDTA) 1:5000 for 5 min at 37 ^{o}C to detach the cells from the flasks. Cells used in electrophysiology experiments are plated on glass cover slips 24–48 h prior to use. hERG current recordings will be performed using the whole cell patch clamp configuration with an Axon MultiClamp 700A amplifier (Axon Instruments, Union City, CA, USA). Voltage clamp protocols are controlled using pClamp9 (Axon Instruments) acquisition and analysis software as previously described [60]. The currents are stable for up to 45 min, and are recorded in control condition and during the application of ZB716 at different concentrations (4–8 cells for each concentration). Borosilicate glass patch pipettes with a tip resistance of 2–4 MO are filled with (mM): KCl 126, $MgSO_4$ 2, $CaCl_2$ 0.5, EGTA 5, Mg-ATP 4 and HEPES 25 (pH 7.3). External bath solution will consist of (mM) NaCl 150, CaCl2 1.8, KCl 4, MgCl2 1, glucose 5 and HEPES 10 (pH 7.4). The temperature will be controlled at 25±0.5 ^{o}C for all experiments using a temperature controller. Sotalol, aspirin and amoxicillin will be dissolved directly in the external bath solution to the desired concentrations. ZB716 is prepared as either a 10 or 100 mM stock solution in DMSO. On the day of experiments, the stock solution will be diluted to the desired concentrations with bath solution. The final concentration of DMSO in bath solution will be 0.1%.
The inhibition of hERG is determined by measuring the peak amplitude of the tail currents at -40mV before and after compound application. The half-maximal inhibitory concentration (IC_{50}) is determined from a curve fit of Hill equation to the data points:

$$Y = (100\% x [ZB716]^{n})/([IC50]^{n} + [ZB716]^{n})$$

where *Y* is the percent inhibition and *n* is a coefficient that determines the slope of the curve.

<u>Aim 3b.</u> Investigate the liver microsomal metabolic profile of ZB716 and determine the excretion pattern of ZB716 after oral administration to mice and rats at various time intervals.

Liver microsomal incubation with NADPH (phase 1 metabolites)
ZB716 will be separately incubated with liver microsomes of mice, rats, dogs, and humans under the same conditions. The incubation mixture, in 0.05 M Tris-HCl buffer (pH 7.4), consists of 2 mg protein/mL liver microsomes, 100 mM valnemulin, and 1 mM NADPH with the total volume of 500 mL. After 2 h of incubation at 37 °C in a metabolic shaker, the reaction will be terminated by adding 500 µL of ice-cold acetonitrile. After centrifugation at 12000 rpm at 4 °C for 15 min, the supernatant will be filtered through a 0.22 µm microbore cellulose membrane into an autosampler vial and analyzed by UHPLC-Q-Exactive (high resolution MS/MS system, Thermo Scientific) for identification of metabolites. Parallel controls include the absence of NADPH and incubation without ZB716, respectively. All experiments will be conducted in triplicate.

Glucuronidation and sulfation profiling (phase 2 metabolites)
UGT-1A is a uridine diphosphate glucuronosyltransferase (UDP-glucuronosyltransferase, UDPGT), an enzyme of the glucuronidation pathway that transforms small lipophilic drugs into water-soluble, excretable metabolites. We propose to profile the glucuronidation pathway of ZB716 by incubating the compound with human liver microsomes in the presence of UGT-1A. Briefly, a pre-incubation solution will be prepared by adding 205 µL water, 24 µL of UGT Reaction Mix solution A, 60µL of UGT Reaction Mix solution B, 7.5 µL human liver microsomes into a 1.5 mL microcentrifuge. The mixtures will be incubated at 37◦C for 5 min followed by adding 3 µL of a 10 mM ZB716, and incubated at 37◦C for 60 min. To terminate the incubation reaction, 300 µL MeOH will be added. The final mixture is then centrifuged at 10,000× g for 4 min at 4◦C. The supernatant will be analyzed on a UHPLC with a high resolution mass spectrometer (Q-Exactive).

For sulfation pathway of ZB716 we will use human liver cytosols supplemented with 3'-Phosphoadenosine-5'-phosphosulfate (PAPS). A pre-incubation solution will be prepared by adding 13.5 µL of 1M pH=7.5 Tris-HCl buffer, 248 µL of water, 6 µL of 1 mM PAPS solution, 30 µL (10 mg/mL) cytosolic protein into a 1.5 mL microcentrifuge. The mixtures will be incubated at 37 ^{o}C for 5 min. Then 3µL of 10mM ZB716 will then be added, mixed, and incubated at 37°C for 60 min. The reaction will be terminated by adding 300 µL MeOH to the mixture, followed by centrifugation at 10,000× g for 4 min at 4 ^{o}C. The supernatant will be analyzed on a UHPLC with a high resolution mass spectrometer (Q-Exactive, Thermo Scientific).

In vivo metabolic profiling

To identify all major metabolites in vivo we will treat mice and rats with single oral dose of ZB716 at 10 mg/kg and collect plasma samples at 2, 4, and 8 hrs post drug administration. The animals will be placed in metabolic cages to collect urine and feces at 8, 24, and 48 hours post drug administration. The plasma, urine, and feces samples will be analyzed using a UHPLC coupled with a Q-Exactive high resolution mass spectrometer.

Aim 3c. Determine ZB716 bioavailability by conducting single dose pharmacokinetics with i.v. arm and repeated dose pharmacokinetics in rats and dogs.

We will perform single dose pharmacokinetic studies in both rats and dogs with an i.v. arm to obtain absolute oral bioavailability data. Serial PK blood samples for analysis of ZB716 and its metabolites in plasma will be collected in all treatment groups (Table 5). Repeat dose PK will also be conducted in two species to obtain dependent pharmacokinetic and to determine dose if ZB716 exhibits linear increase pattern in plasma levels (Table 6). The PK studies in rats will be conducted at Xavier's animal facility while those in dogs will be done by a contract lab (e.g., Redacted by agreement on a fee for service agreement. These studies will provide important bioavailability and pharmacokinetic data for further preclinical evaluation of ZB716 in GLP 28 day toxicology and toxicokinetic studies in rodents and dogs.

Table 5. Single Dose PK with i.v. Arm (rat and dog)

Species	Dose Route	No. animals/ dose group	Total No. of Dose Groups
SD Rats	Oral	6	5 (1 mg/kg–100 mg/kg)
	i.v. injection	5	1 (1 mg/kg)
Beagle Dogs	Oral	3	3 (1 mg/kg – 30 mg/kg)
	i.v. injection	3	1 (1 mg/kg)

Table 6. Repeat Dose PK in Rats and Dogs

Species	Dose Route	No. animals/ dose group	Dose Frequency	Collection Time points
SD Rats	Oral	6	Once daily for 7 days	Pre-dose and post-final dose
				Post-final dose for 6 time pts (0.5, 1, 2, 4, 8, 12, 24 hrs)
Beagle Dogs	Oral	4 males/ 4 females	Once daily for 7 days	Pre-dose and post-final dose
				Post-final dose for 6 time pts (0.5, 1, 2, 4, 8, 12, 24 hrs)

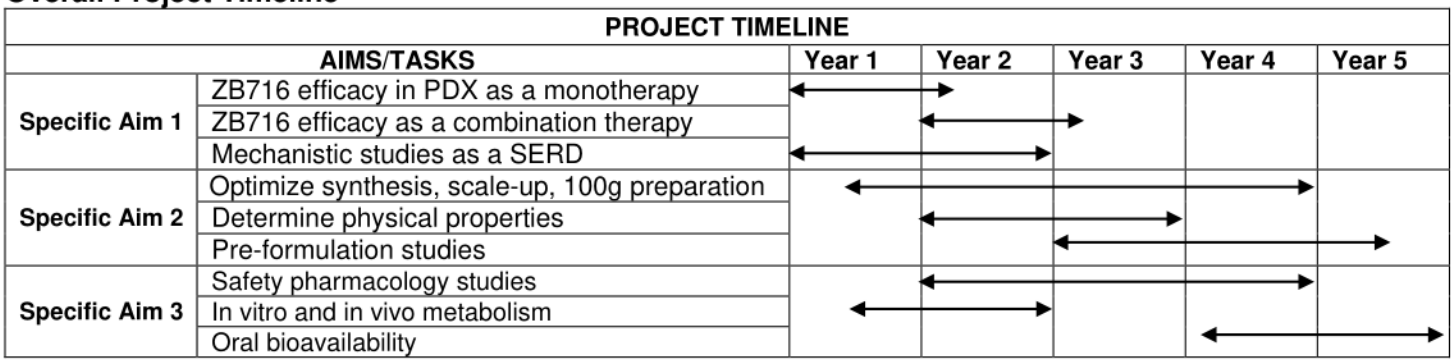
Potential Pitfalls and Alternative Strategies

We expect some challenges in the process improvement experiments to identify better, alternative solvents/reagents to replace existing ones and in finding optimal recrystallization conditions to eliminate chromatography purifications. We realize that for a potential drug candidate being developed for clinical trials, such process improvements will continue well into the GMP manufacturing stage, but also are mindful of the advantages of making early laboratory progress on robust methods of preparation for ZB716. In the event that proposed process improvement experiments do not all result in desired outcomes, we will use the existing synthetic protocols to generate ~100 g ZB716 which will be needed in all proposed in vitro and animal studies while seeking fee-for-service collaborations with contract labs for synthetic optimization expertise in scalable GMP manufacturing.

Expected Outcomes

Accomplishing the proposed aims will provide critical efficacy data to determine whether ZB716 is effective in treating endocrine resistant, ESR1 mutant breast cancer and whether it is a true antiestrogen and ER degrader by acting through the ER. The studies will also demonstrate the potential clinical utility of ZB716 as a combination therapy when used with a CDK4/6 inhibitor. Moreover, synthetic method optimization will pave the way for scalable manufacture of the API and fulfill IND-enabling data on safety pharmacology and physical chemical properties. Collectively, the proposed research will significantly advance the promising oral SERD towards clinical trials to test its safety and efficacy in breast cancer patients.

Overall Project Timeline



Publications Reported for this Reporting Period

NIH Public Access Compliance	Citation
Complete	Toro TB, Painter RG, Haynes RA, Glotser EY, Bratton MR, Bryant JR, Nichols KA, Matthew-Onabanjo AN, Matthew AN, Bratcher DR, Perry CD, Watt TJ. Purification of metal-dependent lysine deacetylases with consistently high activity. Protein Expr Purif. 2018 Jan;141:1-6. doi: 10.1016/j.pep.2017.08.009. Epub 2017 Aug 24. PubMed PMID: 28843507; PubMed Central PMCID: PMC5624855.
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In process at NIHMS	Yao X, Gray S, Pham T, Delgardo M, Nguyen A, Do S, Ireland SK, Chen R, Abdel-Mageed AB, Biliran H. Downregulation of Bit1 expression promotes growth, anoikis resistance, and transformation of immortalized human bronchial epithelial cells via Erk activation-dependent suppression of E-cadherin. Biochem Biophys Res Commun. 2017 Nov 21. pii: S0006-291X(17)32305-7. doi: 10.1016/j.bbrc.2017.11.126. [Epub ahead of print] PubMed PMID: 29170133. [Epub ahead of print]
In process at NIHMS	Pham D, Cormick G, Amyx MM, Gibbons L, Doty M, Brown A, Norwood A, Daray FM, Althabe F, Belizán JM. Factors associated with postpartum depression in women from low socioeconomic level in Argentina: A hierarchical model approach. J Affect Disord. 2017 Nov 21;227:731-738. doi: 10.1016/j.jad.2017.11.091. [Epub ahead of print] PubMed PMID: 29179143. [Epub ahead of print]
Complete	Zhang W, Edwards A, Flemington EK, Zhang K. Racial disparities in patient survival and tumor mutation burden, and the association between tumor mutation burden and cancer incidence rate. Sci Rep. 2017 Oct 20;7(1):13639. doi: 10.1038/s41598-017-13091-y. PubMed PMID: 29057889; PubMed Central PMCID: PMC5651797.
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In process at NIHMS	Echeverri M, Anderson D, Nápoles AM. Assessing Cancer Health Literacy among Spanish-Speaking Latinos. J Cancer Educ. 2017 Jul 24. doi: 10.1007/s13187-017-1255-y. [Epub ahead of print] PubMed PMID: 28741268. [Epub ahead of print]
In process at NIHMS	Gross TT, Story CR, Harvey IS, Allsopp M, Whitt-Glover M. "As a Community, We Need to be More Health Conscious": Pastors' Perceptions on the Health Status of the Black Church and African-American Communities. J Racial Ethn Health Disparities. 2017 Jul 13. doi: 10.1007/s40615-017-0401-x. [Epub ahead of print] PubMed PMID: 28707267. [Epub ahead of print]
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Complete	Hossain A, Tauhid L, Davenport I, Huckaba T, Graves R, Mandal T, Muniruzzaman S, Ahmed SA, Bhattacharjee PS. LRP-1 Pathway Targeted Inhibition of Vascular Abnormalities in the Retina of Diabetic Mice. Curr Eye Res. 2017 Apr;42(4):640-647. doi: 10.1080/02713683.2016.1203441. Epub 2016 Jul 21. PubMed PMID: 27442082; PubMed Central PMCID: PMC5499693.
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PMC Journal In Process	Story CR, Gross TT, Harvey IS, Whitt-Glover MC. Pastoral perceptions of the learning and developing individual exercise skills (L.A.D.I.E.S.) intervention: a qualitative study. Health Educ Res. 2017 Feb 1;32(1):81-95. doi: 10.1093/her/cyw054. PubMed PMID: 28052931.

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Complete	Efird JT, Gudimella P, O'Neal WT, Griffin WF, Landrine H, Kindell LC, Davies SW, Sarpong DF, O'Neal JB, Crane P, Nelson MA, Ferguson TB, Chitwood WR, Kypson AP, Anderson EJ. Comparison of Risk of Atrial Fibrillation in Black Versus White Patients After Coronary Artery Bypass Grafting. Am J Cardiol. 2016 Apr 1;117(7):1095-100. doi: 10.1016/j.amjcard.2015.12.056. Epub 2016 Jan 15. PubMed PMID: 26857161; PubMed Central PMCID: PMC4799751.
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Proposed Animal Protocol for Pre-clinical Studies of ZB716

1. Description of Procedures.

Efficacy Studies

This project includes studies of the pharmacology, bioavailability, and ADME of an orally bioavailable selective estrogen receptor downregulator (SERD). Currently, fulvestrant is the only FDA approved SERD indicated for advanced metastatic breast cancer either as a first line regimen or as treatment for progressing disease after tamoxifen or AI therapy. Fulvestrant has very poor bioavailability and its oil-based injection only route of administration limits both its therapeutic efficacy and widespread clinical use. Development of orally bioavailable SERDs to improve therapeutic efficacy and overcome low bioavailability and other disadvantages associated with i.m. injection is urgently needed. Zenopharm has recently designed, synthesized, and tested an orally bioavailable steroidal SERD (ZB 716) that demonstrated excellent peak plasma concentration and increased t½ and area under curve (AUC) values. Compared to fulvestrant at equal dosage by s.c. injection, ZB716 afforded over 10-fold higher serum drug concentration in mice. If such enhancement of oral bioavailability can be translated to humans, ZB716 holds the promise of being a viable oral SERD, with increased therapeutic efficacy and more durable treatment outcome than the current SERD regimen.

We propose dose-finding efficacy studies of ZB716 in five PDX breast tumor models as an orally administered drug, in comparison with fulvestrant s.c., at various dose levels and determine the therapeutically effective dose range and if there is a toxicity-limiting dose in tumor-bearing mice. The five WHIM PDX tumor lines (Table 1) are well established models[1,2] obtained from Washington University that include both luminal A and luminal B subtype, and wild type ESR1 as well as mutant ESR1 genotypes. One PDX (WHIM11) is derived from primary tumor but is estrogen-independent, representing patients unlikely to benefit from SERM/AI treatment but can be potentially treated with SERD as a first line endocrine therapy. WHIM26 represents an advanced metastatic yet E2-dependent setting to test ZB716 efficacy compared to SERM/AI treatment. WHIM9 retains wild type ER but is a recurring E2 independent phenotype for which SERD may be the only option as endocrine therapy. Both WHIM20 and WHIM18 are progressed diseases with ER mutants and thus E2 independent for which SERD efficacy is crucial.

Table 1: PDX model characteristics

PDX model	Subtype (PAM50)	Donor race	ESR1 genotype	E2-dependent	Site of biopsy
WHIM26	Luminal A	White	WT	Yes	Node metastasis
WHIM11	Luminal B	White	WT	No	Primary
WHIM9	Luminal B	AA	WT	No	Skin metastasis
WHIM20	Luminal A	White	Y537S	No	Skin metastasis
WHIM18	Luminal B	AA	YAP1	No	Skin metastasis

Each model will involve 6 treatment arms as shown in Table 2. Using the GPower software and selecting effect size of 0.5, 80% power, α=0.05, and # of groups=6, the total sample size is calculated to be 60 mice, or 10 mice/ group in one model study. Thus the total number of mice required for five PDX models will be 5x60=300 mice.

Table 2. PDX Treatment arms, dose finding experiment

Treatment Arm	Vehicle	Fulvestrant	ZB716
Control	+	-	-
Fulvestrant	-	250mg/kg/wk sc	-
ZB716 – Dose level 1	-	-	5 mg/kg po qd
ZB716 – Dose level 2	-	-	10 mg/kg po qd
ZB716 – Dose level 3	-	-	30 mg/kg po qd
ZB716 – Dose level 4	-	-	50 mg/kg po qd

[1] Li S, Shen D, Shao J et al, Endocrine-therapy-resistant ESR1 variants revealed by genomic characterization of breast-cancer-derived xenografts. Cell Rep. 2013 Sep 26;4(6):1116-30.

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Combination efficacy studies of ZB716 with palbociclib in PDX breast tumor models

We will study the efficacy of ZB716 in combination with palbociclib (CDK4/6 inhibitor). After showing clinically significant improvement in median progression free survival (PFS) in PALOMA-3 international phase 3 trial, FDA approved palbociclib (Ibrance, Pfizer) for use in combination with fulvestrant for the treatment of women with hormone receptor (HR)- positive, HER2-negative advanced or metastatic breast cancer (MBC) with disease progression following previous endocrine therapy[3]. This latest development represents a significant advance in the treatment of metastatic HR-positive breast cancer which effectively expands the clinical utility of SERDs. We hypothesize that an oral SERD could offer even more pronounced clinical benefits given its greater bioavailability and drug exposure level. As shown in Table 3, the doses of palbociclib were chosen based on the recent literature on non-steroidal SERM preclinical characterization[2].

Table 3. Treatment arms for combination experiments

Treatment Arm	Vehicle	Fulvestrant	ZB716	Palbociclib
Control	+	-	-	-
Fulvestrant	-	5 mg/wk sc	-	-
ZB716	-	-	MED* po qd	-
Fulvestrant/palbociclib	-	5 mg/wk sc	-	-
ZB716/palbociclib	-	-	MED* po qd	45 mg/kg po qd

*MED = minimum effective dose

Pharmacokinetics and metabolism studies

Metabolism studies will be performed in mice and rats in which animals will be housed in metabolic cages to collect urine and feces. We will perform pharmacokinetic and metabolism studies in both rats and dogs with an i.v. arm to obtain absolute oral bioavailability data. Serial PK blood samples for analysis of ZB716 and its metabolites in plasma will be collected in all treatment groups (Table 4). Repeat dose PK will also be conducted in two species to obtain dose dependent pharmacokinetic and to determine if ZB716 exhibits linear increase pattern in plasma levels (Table 5). The PK studies in rats will be conducted at Xavier's animal facility while those in dogs will be done by a contract lab Redacted by agreement on a fee for service agreement.

Table 4. Single Dose PK with i.v. Arm (rat and dog)

Species	Dose Route	No. animals/ dose group	Total No. of Dose Groups
SD Rats	Oral	6	5 (1 mg/kg–100 mg/kg)
	i.v. injection	5	1 (1 mg/kg)
Beagle Dogs	Oral	3	3 (1 mg/kg – 30 mg/kg)
	i.v. injection	3	1 (1 mg/kg)

Table 5. Repeat Dose PK in Rats and Dogs

Species	Dose Route	No. animals/ dose group	Dose Frequency	Collection Time points
SD Rats	Oral	6	Once daily for 7 days	Pre-dose and post-final dose
				Post-final dose for 6 time pts (0.5, 1, 2, 4, 8, 12, 24 hrs)
Beagle Dogs	Oral	4 males/ 4 females	Once daily for 7 days	Pre-dose and post-final dose
				Post-final dose for 6 time pts (0.5, 1, 2, 4, 8, 12, 24 hrs)

2. Justifications.

Justification for use of animals

The project is designed in such a way as to minimize the use of mice. We have tested extensively in cellular systems the dose range and mechanisms of action of the drug candidates, and have narrowed down to one single most promising oral drug for in vivo testing which is required of pre-clinical proof of concept experiments. For single dose and repeated dose pharmacokinetic studies,

[3] Walker AJ, Wedam S, Amiri-Kordestani L, Bloomquist E, Tang S, Sridhara R, Chen W, Palmby TR, Fourie Zirkelbach J, Fu W, Liu Q, Tilley A, Kim G, Kluetz PG, McKee AE, Pazdur R. FDA Approval of Palbociclib in Combination with Fulvestrant for the Treatment of Hormone Receptor-Positive, HER2-Negative Metastatic Breast Cancer. Clin Cancer Res. 2016 Oct 15;22(20):4968-4972

Sprague Dawley rats and beagle dogs will be used with rats study done at Xavier and dogs study done by a contract lab on a fee for service basis. Bioavailability cannot be determined by in vitro method because the concentration of the active ingredient in systemic circulation of an animal is required in pharmacokinetic studies. In addition, to proceed into clinical trials, in vivo data for both pharmacokinetics and efficacy must be obtained.

The goal of this proposal is to determine the in vivo efficacy of ZB716 to inhibit ER+ breast cancer using patient derived xenograft models. In vitro studies using tamoxifen resistant MCF-7 cells have demonstrated that the ZB716 are effective in inhibiting the growth and proliferation of the estrogen dependent, but tamoxifen resistant breast cancer cells (MCF-7/TamR). In order for the drug candidates to move towards eventual clinical trials, the next critical step is to show in vivo efficacy in the most clinically relevant animal models. Moreover, we need to show that orally administered ZB716 can achieve equivalent or better tumor suppression effect compared to the standard treatment of fulvestrant s.c. injection. Mice will be used because of their short gestation time, well-defined genetics, and well-developed procedures for xenograft models.

Justification for the use of immunocompromised mice
We must use animals with compromised immune systems in order to prevent rejection of the xenografted human breast cancer cells and subcutaneous tumors are easily visualized in the nude mouse. These models are well-established for studies of tumorigenesis, and have been used in the study on effects of chemotherapeutics, anti-estrogens, and targeted anticancer therapies.

Justification for the use of female mice
The mouse xenograft models will host patient derived human breast tumors expressing either wild type estrogen receptor or mutant ESR1, and some may require the use of estrogen pellets to supply estrogen to mice in order to maintain the growth of the xenograft tumors. Only female mice can accommodate a sustained circulation level of estrogen. In addition, to mimic tumor growth environment in humans, the xenograft is best seeded in the mammary fat pad (MFP) of female mice. Thus female mice have been almost exclusively used in the in vivo study of human breast cancer in animals.

3. Minimization of Pain and Distress.
To minimize pain and discomfort, mice will be sedated with ketamine/xylazine and $5x10^6$ cancer cells will be injected into the mammary fat pads (bilaterally, i.e., 2 injections per animal).
Selective estrogen receptor downregulators are not known to have acute toxicities in nude mice based on literature reports when used at therapeutically effective doses. In the proposed dose range of 5 mg/kg to 50 mg/kg, It is unlikely that any acute toxicities will be observed. However, animals will be closely monitored for any sign of lethargy and significant weight loss (>15% of TBW). Mice showing such symptoms will be taken off study medication and humanely euthanized.

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Resource Sharing Plans

Data Sharing Plan

What data will be shared
The following data will be shared through publication on peer-reviewed journals:

1. Method of synthetic preparation of ZB716 and any modifications to procedures that have already been published
2. Method of analysis of ZB716 and its associated metabolites, including methods of identification and quantification in biological samples such as tissue and blood.
3. Pharmacokinetic data of ZB716 in rats and dogs
4. Toxicological and toxicokinetic data in rats and dogs.

The following data will be shared through patent filing:

1. Process of scaled-up synthesis and manufacture of ZB716
2. Formulation studies

Who will have access to the data
Any investigators will have access to the data through PubMed free PMC article deposits.

Where will the data to be shared be located
The above described data resulting from this grant will be detailed in scientific manuscripts, which upon acceptance for publication by journals will be deposited as free PMC articles. Where applicable, additional relevant experimental data will be included in the Supporting Information associated with published manuscripts.

When will the data be shared?
The manuscripts describing these data will be submitted for publication as soon as possible; the manuscripts will be deposited for free access on PubMed upon acceptance for publications.

How will researchers locate and access the data?
I agree that I will identify where the data will be available and how to access the data in any publications and presentations that I author or co-author about these data, as well as acknowledge the repository and funding source in any publications and presentations.

Sharing Model Organisms

N/A

Genomic Data Sharing (GDS)

N/A

Authentication of Key Biological and/or Chemical Resources

Key Biological Resources

1. Breast Cancer Cell Models

To ensure that the breast cancer cell lines remain phenotypically identical without any contamination, we will authenticate the cell lines by Short Tandem Repeat (STR) before using them to form xenograft tumors in mice. We will use the Complete Human Cell Line Authentication Service available at ATCC. Briefly, cell samples will be sent to ATCC using the sample kit from ATCC where 17 STR loci plus Amelogenin will be amplified followed by a comprehensive analysis report comparing allele calls at each locus against the known reference profiling in the ATCC STR database.

2. Patient-derived xenograft

Patient-derived xenografts of ER+ human breast tumors will be authenticated in our laboratory for any ZB716 efficacy studies as needed. Our laboratory will transplant authenticated clinical tumor tissues by Short Tandem Repeat protocols in nude mice (performed in the Animal Care Facility at Xavier University) before each passaging and propagation batch experiment.

Key Chemical Resources

ZB716 as final product:

Each batch of the drug product from synthetic processes will be authenticated by the following analytical methods in our laboratory:

1. 400 MHz NMR spectrometry analysis to verify the molecular structure.
2. Melting point determination
3. High resolution mass spectrometry to determine and verify accurate mass.
4. High performance liquid chromatography analysis to verify purity.