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TITLE: Training HBCU Faculty and Students in Prostate Cancer (PC) Research: Signal Transduction and Receptor-Inhibitor Interactions in the Progress of PC

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14. ABSTRACT
This program aims to help eradicate prostate cancer (PC) disparity in African Americans through educational and research programs. Our hypothesis is that through PC education and participation in PC research, a meaningful number of African Americans will be able to contribute to the elimination of disparity in PC. Our program comprises three Specific Aims. (1) To develop, promote, and sustain independent, competitive research and training programs at Xavier University. Both projects are moving forward, presenting data and involving students. (2) To increase the number of Xavier University investigators focused on PC research. One new project has been developed and is involving students. (3) To establish a long-term collaborative relationship between Xavier University and the TCC in PC research. XU faculty in the program are now members of the Tulane Cancer Center and involved in weekly seminars and focus group meetings.

15. SUBJECT TERMS
Prostate cancer, signaling pathways, ErbB-2 receptor, ErbB-4 receptor, molecular models, mechanisms of metastasis, NF-KB, P53

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5th Annual Report on Grant #W81XWH-04-1-0252
March 1, 2008 through February 28, 2009

Training HBCU Faculty and Students in Prostate Cancer (PC) Research: Signal Transduction and Receptor-Inhibitor Interactions in the Progress of PC

Thomas E. Wiese, Ph.D.

INTRODUCTION

We intend to help eradicate prostate cancer (PC) disparity in African Americans by targeting this population through educational and research programs. Our hypothesis is that through PC education, exposure to PC issues, and participation in PC research, a meaningful number of African Americans will acquire the knowledge to contribute to the elimination of disparity in PC. Our program comprises three Specific Aims. The first Aim develops, promotes, and sustains independent, competitive research and training programs at Xavier University. This Specific Aim is proceeding on track with both major research projects generating enough data to present at research symposia and both involving students. The second Aim increases the number of Xavier University investigators focused on PC research, to date one Xavier faculty has been matched with an experienced researcher from the Tulane Cancer Center (TCC) and their project is underway and involves Xavier students. The third Aim establishes a long-term collaborative relationship between Xavier University and the TCC in PC research. Xavier faculty involved in this DOD funded PC program are part of a nucleus of Xavier faculty that are now members of the Tulane Cancer Center, the Louisiana Cancer Research Consortium (LCRC) and involved in affiliated weekly seminars and research groups. This program has recovered from Katrina related set backs and delays due to the award of an extra funded program year from DOD. The Xavier and Tulane faculty involved in this DOD program are also developing additional cancer research and education programs with the Tulane Cancer Center and the Louisiana Cancer Research Consortium (LCRC). The primary mechanism for this expanded interaction is an NCI P20 planning grant awarded to Xavier and Tulane in October 2005 to develop additional collaborative research projects, a cancer biology course focused on health disparities for students at Xavier and Tulane, cancer research experiences for Xavier students and mechanisms to integrate health disparities education into the professional curriculums at Xavier and Tulane. Dr. Wiese, the PI of this DOD PC program is the Xavier manager of the NCI P20 grant and Dr. Ireland (Xavier Biology) submitted and was awarded a pilot project in the P20 program in 2006. This NCI program is now fully underway along with this DOD program and the Xavier and Tulane DOD Breast Cancer Program (2004-2009).

BODY

This reports funding period covers March 1, 2007 through February 28, 2008.

The final year of this program has produced one manuscript published, one manuscript in prep, presentations at the AACR meeting and local meetings, student involvement and solid plans to continue the projects. With the addition of the funded extra awarded by DOD, the program has recovered as well as expected from the impacts of Hurricane Katrina. This extra funding also has resulted in significant funds carry over from the Katrina evacuation years. Thus, we have asked for a no-cost extension to continue the programs projects at a smaller scale until Feb 2009. This no-cost extension will allow each project to maintain momentum while other funding is secured.

Significant events in this last year effecting the program include: the loss of one Tulane collaborator (Dr. Frank Jones left Tulane), the loss of one new Xavier investigator (Dr. Duane Johnson died) and the gain of a new Xavier investigator (Dr. KaTani Parker-Johnson). The impact of these events is described in the relevant sections below.

SPECIFIC AIM I

Develop, promote, and sustain independent, competitive research and training programs at Xavier University.

A. Ireland/Abdel-Mageed project: "Genetic Basis of Prostate Cancer: Factors influencing the mortality rates of minorities"

Note:
No year 5 updates on this project were provided by either Dr. Ireland or Dr. Abdel-Mageed after requests in February, April and August 2009. The PI, DR. Wiese, has asked for this report in emails and verbal conversations, each time the project team agreed to get it to the PI right away and each time nothing has happined.

He following citations are related to this teams progress in the last year and have been provide by the program PI:

ACS: #RSGTCCE-116942 (Abdel-Mageed) 4.8 Calendar
7/1/2009-6/30/2013
"Nuclear matrix proteins in ethnic disparity of prostate cancer. ACS "
This application focuses on the interaction of nuclear matrix proteins with AR signaling in progression of prostate cancer in African American men.
Funded.

DOD- PC081598 (Abdel-Mageed) 3.0 Calendar
7/1/2009-6/30/2012
"Molecular Determinants of Disparity of Prostate Cancer"
The objectives of this proposal are to delineate relevant biomarkers associated with prostate cancer progression in African American men**. <u>Funded</u>**

Submitted: June, 2009
NCMHD P20 (Deininger)
Project 1: (Abdel-Mageed, PI): /direct/yr 3.0 Calendar
2/1/2010-1/31/2015
"Interactions between AR and ER Signaling in Disparity of Prostate Cancer"

NIH (U01)- FOA (PAR-09-161) direct/year 3.0 Calendar
4/1/2010-3/31/2015
" Estrogen-ERβ Axis in Disparity of Prostate Cancer"

Publications:
hnRNPH1 and prostate cancer progression in African American men: role in activation of androgen receptor signaling (*in preparation*).

Below is the Y4 report from this project:

1. <u>Search for a replacement technician to assist in project (Months 1- 4)</u>
Dr. Qiuyun Yang did not return to New Orleans after Katrina. After conducting nationwide search, Dr. Padma Sankar was hired in late summer 2006 as a replacement but for various reasons, December 31st 2007 was her last day in the lab. In Fall of 2007, Dr. Zibiao Guo was hired to move the project faster.

2. <u>Identify new student(s) to assist in project (Month 3)</u>
A total of four students were identified to work on various aspects of the project. These were Nazima Yousuf, Chichi Obih, Syed Ahmed and Garrett Anderson

3. <u>Establish a connection between androgen-receptor presence and activity, and drug resistance (Months 1-9)</u>
a. *Establish prostate cancer cell lines (Month 1)*
Dr. Ireland has re-established three prostate cancer (CaP) cell lines at Xavier University's cell culture facility. They include PC-3, DU-145 (both androgen independent) and LNCaP (androgen dependent). These cells were lost during the Katrina evacuation and all cell culture capacity in the Ireland lab was re-established in Summer 2006.

b. *Test the effect of radiation and chemotherapy on apoptosis (Months 2-5)*
(See I.A.4)
c. *Test the effect of radiation and chemotherapy on growth (Months 6-9)*
(See I.A.4)

4. Identify the relation between NF-kB and p53 in establishing drug-resistance phenotype in CaP cells (Months 10-21).

To further identify the relationship between NF-κB (a transcription factor and an antiapoptotic agent) and p53 (also a transcription factor and apoptotic tumor suppressor gene), the NF-κB luciferase reporter assays were conducted in both DU-145 and PC-3 cell lines. While NF-κB is constitutively activated in both cell lines, PC-3 cells are p53-deficient whereas DU-145 express mutant p53. Hence the assay was designed to determine the possible effects of exogenous, wild-type p53 on NF-κB. To accomplish this, CaP cells were co-transfected with appropriate plasmids (the control CMV plasmid, the NF-κB-luc plasmid and the p53 wild type plasmids) and the assays were conducted in presence and in the absence of TNF-alpha, known inducer of endogenous NF-κB and wild type adenovirus or IkB super-repressor adenoviral vector, an inhibitor of NF-κB activation. Additional transfections and assays were performed in LNCaP cells in presence of CBP/p300 (coactivator for p53 dependent transactivation and repression). Using the luciferase reporter assays, the NF-κB activation was measured by a fluorometer relative to the normalized levels of endogenous beta-galactosidase activity in each cell line. The results demonstrated that the wild-type p53 inhibits NF-κB activation by an average of 40 % in the absence of TNF-alpha, the endogenous NF-κB inducer. In the presence of TNF-alpha, this inhibition increased to more than 50 %. Using reporter assays, restoring wild-type p53 inhibited TNF-α-induced p65-luciferase activation in PC-3 and DU-145, but not LNCaP, cell lines. These observations were confirmed by Western blot and gel shift analyses. Contrary to our expectations, overexpression of p65 in these cells increased luciferase activity driven by truncated promoter encompassing p53-binding motifs; an effect which was partially inhibited by co-transfection of wt p53. The results were further confirmed by p65-induced transactivation of p21 promoter, driven by two p53-binding motifs, in PC-3 cells. Deletion mutation analysis in PC-3 cells demonstrates that p65 mediates p21 transactivation via a p53-binding motif. Taken together, the results suggest that p53 DNA binding motif is required for NF-κB activation of p53 regulated genes in PC cells lacking or expressing mutated p53 gene. The clinicopathological role of selective NF-κB activation of p53-regulated genes in PC remains to be elucidated.

a. *Measure p53 in sensitive and resistant cell lines and PC tissues from biracial populations (Months 10-15).*

This aim has been delayed by 6-12 months due to Katrina

b. *Measure NF-kB in sensitive and resistant cell lines and PC tissues from biracial populations (Months 10-15)*

This aim has been delayed by 6-12 months due to Katrina.

c. *Measurement of NF-kB-induced expression of anti-apoptotic proteins (Months 16-21)*

5. Test if chemoresistance is mediated via crosstalk between NF-kB and p53 (Months 22-36)

When the luciferase reporter assays were conducted in the presence of wild type adenovirus or adenoviral vector, the results showed that the p53 inhibition of NF-κB increased by more than 10 fold in PC-3 and DU-145 cells. These observations in PC-3 and DU-145 cells were confirmed by Western blot analyses. In LNCap cells (androgen receptor positive with mutated p53), the above-mentioned inhibitors actually lost their inhibitory effect on NF-κB. These observations suggest that androgen receptor may be involved in modulating the IkB super-repressor adenoviral inhibitory function. Reproducible results showed that NF-κB inhibits p53 in PC-3 and DU-145 cells. Results from additional assays conducted in presence of

CBP/p300 (coactivator for p53 dependent transactivation and repression) suggest that that this coactivator is involved in the mutual inhibitory effects of NF-κB and p53 in prostate cancer cells.

a. *Test p53 level and activity after blocking NF-kB (Months 22-27)*
b. *Test p53 level and activity after activating NF-kB. (Months 28-30)*
c. *Test if changes in NF-kB status affect p53 status in PC cell lines. (Months 31-36)*

6. Deliverables/measurable outcomes: Dr. Ireland will prepare or oversee the following:
a. *Semiannual reports will be submitted to the Co-PI*
Dr. Ireland has submitted one report in Y3.

b. *One abstract will be submitted to a professional conference each year (Months 12, 24, 36)*
Data has been accepted for presentation of the 2008 Annual Meeting of the AACR in San Diego, CA., April, 2008 Abstract Number #2934: Selective Activation of p53-Regulated Genes by NF-κB in p53-deficient and – mutated Prostate Cancer Cells. S. P. Kale, P. Sankar, Q. Yang, C. Zibao, A. B. Abdel-Mageed

c. *Students involved in the research will present a poster at the annual research workshop (Months 12, 24, 36)*
The schedule of the two new students allowed them little time in the lab which was spent in the training and repeating the previous experiments (for reproducibility). They will present in the next few months at a regional or national meeting.

d. *One competitive grant application will be submitted by end of Month 24*
Plans are unchanged.

e. *One paper will be submitted by end of Month 36*
One manuscript is in preparation and is expected to be submitted shortly.

Plans beyond Feb 2008 - Dr. Zibiao Guo will continue working with Drs. Abdel-Mageed and Ireland to identify NF-κB activation of p53 regulated genes in PC cells and explore the potential for androgen receptor to regulate these genes.

B. **Stevens/Jones project: "The Search for Tyrosine Kinase Inhibitors (TKIs) of Prostate Cancer Cell Growth"**

B. **Stevens/Jones project: "The Search for Tyrosine Kinase Inhibitors (TKIs) of Prostate Cancer Cell Growth"**
1. Hire technician to assist in project (Month 1)
Tracy Kirksey was hired within one month of initiating this project. She has a B.S. degree in Chemistry from Xavier University. Her primary responsibilities are (1) to grow and maintain the prostate cancer cell lines and (2) to test compounds as prospective inhibitors of ErbB2 tyrosine kinase activity. Because Dr. Stevens has just been elected chair of the Department of Chemistry at Xavier University, she plans to hire another technician to work alongside Ms. Kirksey, performing the molecular modeling studies.

Tracy Kirksey did not return to Xavier after Hurricane Katrina. Ping Jin was hired as a Research Associate in May 2005 to work on the molecular modeling portion of this project (CV included as Appendix #3). Her responsibilities include database mining, building a homology model of the tyrosine kinase enzyme, and docking potential inhibitors.

Ping Jin left Xavier to move to Texas with her husband in April 2008. She was able to complete the tyrosine kinase homology model of HER2, database mining using the quinazoline and tyrphostin pharmacophores, and docking and virtual screening of those compounds.

2. Identify student to assist in project (Month 3)

Joseen Bryant, a chemistry major, was hired within one month of the start of this project. Her primary responsibilities are to use the SYBYL molecular modeling software package to develop a pharmacophore that can be used to search databases for new compounds to be tested for tyrosine kinase inhibition. Dr. Stevens is adding three additional students to this project. The first, Nicole Bell, is a Graduate Alliance for Education in Louisiana (GAELA)/American Chemical Society Scholar. She has already contributed significantly to this project, solving the two x-ray crystal structures described in Aim I.B.3. Ms. Bell will be supported in part as a Slayton Evans Summer Research Scholar. The other two students are Nyote Oliver, who is a MARC Scholar, and Shelley Schmidt.

Joseen Bryant did not return to Xavier after Hurricane Katrina. Nicole Bell has continued to work on the crystal structures of tyrosine kinase inhibitors. A senior, Aviva Baird, has joined the group and will begin working on the CoMFA study.

March 2007 - Both Nicole and Aviva graduated from Xavier. Both are attending graduate school in the chemical sciences. Torrey Fingal was hired in November 2006 to work on this project. He has been trained in x-ray crystallography and will begin working on the molecular modeling component this summer. Peter Tran, a MARC scholar, has also joined the group and has been working on the x-ray crystallography.

February 2008 – Peter Tran has contributed significantly to this project. He solved six crystal structures described in Aim I.B.3. In addition he spent the summer 2007 learning techniques in small molecule QSAR. He completed one ComFA study on the tyrphostin series of compounds and has begun another CoMFA study on the quinazoline series of compounds.

May 2008 – Iris Alao, Ryan Graham, and Sean Haron were hired and trained in cell proliferation techniques. They grew MCF7 cancer cells and tested the prospective inhibitors of cell growth identified by the Stevens lab using an alimar blue assay.

3. Identify novel small molecules that inhibit ErbB2 activity related to among quinazoline, pyrimidine, and quinoline derivatives (Months 1-18)

a. *Determine X-ray crystal structures of known tyrosine kinase inhibitors (quinazoline, pyrimidine, and quinoline derivatives) (Months 1-12)*

The x-ray crystal structures of a third tyrosine kinase inhibitor has been completed. This is N-(3',4'-dihydroxybenzylidenecyanoacetyl)indoline, a tyrphostin derivative. Crystals were obtained by slow evaporation of solvent and x-ray diffraction data were collected at room temperature on an Enraf-Nonius CAD4 diffractometer with a molybdenum target x-ray tube. Data were refined on a LINUX workstation with the maXus software package (Bruker Instruments). The structures are included as Appendix A-4. The Stevens group continues to recrystallize available tyrosine kinase inhibitors. As crystals are obtained, they will collect x-ray diffraction data for these compounds. These x-ray crystal structures will be used as reference structures for the molecular modeling results.

March 2007 - Three more x-ray crystal structures of 4-methoxybenzylidenemalononitrile, α-cyano-(3,5-di-t-butyl-4-hydroxy)thiocinnamide, and 4-[(3-bromophenyl)amino]-6-propionylamidoquinazoline have been completed. We continue to crystallize samples of tyrosine kinase inhibitors.

February 2008 – Two more x-ray crystal structures of 3,5-di-t-butyl-4-hydroxy)malononitrile and 4-[(3-chlorophenyl)amino]-6,7-dimethoxyquinazoline have been completed. We continue to crystallize samples of tyrosine kinase inhibitors.

February 2009 – X-ray crystal structures of 6,7-dimethoxyquinaxaline and α-cyano-(3,4-dihydroxy)cinnamide have been completed.

b. *Identify detailed pharmacophore and determine geometric, electronic, and lipophilic characteristics required for tyrosine kinase inhibition using*

Comparative Molecular Field Analysis quantitative structure activity relationships (Months 1-12)

An extensive literature search was used to identify small molecules that are known to inhibit ErbB2 activity. These molecules are related to quinazolines, pyrimidines, quinolines, and tyrphostins. Dr. Stevens has collected a library of molecules that have been divided into two sets. One set includes 31 tyrphostins whose EGFR and ErbB2 activities were measured by Gazit and Levitzki.[1-3] The second set includes 71 quinazolines and similar molecules whose activities were measured by Wissner.[4-6]

Using the molecules with known activity against prostate cancers cell lines, a third pharmacophore model has been developed (see Appendix A-5). This pharmacophore model along with the two that had been developed last year identify the geometric relationship between structural features of a set of molecules known to act as tyrosine kinase inhibitors.

c. *Identify new compounds to be tested for tyrosine kinase inhibition with conformationally flexible searches of compound databases using detailed pharmacophore and CoMFA QSAR results (Months 9-18)*

The geometric models noted in I.A.3.b have been used to search databases for new compounds having the same geometric arrangement of structural features but not yet been identified as tyrosine kinase inhibitors. These databases have been installed and are available for searching at Xavier University. They include the Available Compounds Database (Molecular Design Limited), the National Cancer Institute Database, the EPA Toxic Chemicals Database, and the SMILE CAS Database. Software available for database searching includes HiVol and Unity (part of the SYBYL software package).

Preliminary searches with successive filtering yielded several hundred prospective compounds. Additional virtual compound screening by docking these compounds into a homology model of the receptor is planned. A Comparative Molecular Field Analysis (CoMFA) QSAR study of the quinazoline derivatives has begun. Because of delays imposed by Hurricane Katrina, Dr. Stevens plans to complete this study by August 2006. The database has been created with nearly 80 molecules. The structures of all molecules have been optimized and MOPAC charges have been calculated. The most difficult part of the study has been to obtain an appropriate alignment of all molecules in the database. Dr. Stevens plans to begin the database search using the pharmacophore models developed during the past year. At that point, she will use the CoMFA model results to search for additional compounds that might be active as tyrosine kinase inhibitors.

February 2008 – A CoMFA model calculated from 80 quinazoline derivatives is nearly complete. Each molecule was subjected to a conformational search in which 10 alternate conformations were calculated and stored in a database. All molecules and conformations were included in the molecular alignment and a statistically significant CoMFA model has been generated.

February 2009 – The CoMFA model was generated by Peter Tran. It remains to be validated.

4. <u>Explore the mechanism of ErbB2 tyrosine kinase inhibition (Months 13-24).</u>

Plans are unchanged.

a. *Build a homology model of the ErbB2 tyrosine kinase ATP binding site.*

(Months 13-18) March 2006 - Dr. Stevens' group has begun learning how to build homology models using the Composer module in SYBYL 7.1. They have used this software package to build a homology model of P450 2B1 using the protein crystal structures of P450 2B4 as templates with the sequence of P450 2B1 used as the target. The initial model was refined and submitted to a series of tests to determine its quality and consistency using Procheck and ProsaII.

March 2007 - A homology model of ErbB2 was built based on three protein crystal structures (Epidermal Growth Factor Kinase Domain (1M14), Epidermal Growth Factor Receptor Kinase Domain with bound erlotinib (TercevaTM) (1M17), and Epidermal Growth Factor Receptor Kinase Domain with bound GW572016 (LapatinibTM) (1XKK)) which are available from the Protein Data Bank. The sequence of human ErbB2 was obtained from the SwissProt database and was used as the target. The Composer module in SYBYL 7.1 was used to construct the three-dimensional model of ErbB2. The initial model was refined by minimizations carried out by the 2000 steps of steepest descent method followed by the conjugate gradient method until the root mean square gradient of the potential energy was < 0.05 kcal/mol Å. The minimized homology model was

validated using Procheck and ProsaII. The results showed that our homology model is consistent with a good quality structure comparable to a high resolution X-ray structure.

b. *Dock proven and proposed TKIs into the tyrosine kinase ATP binding site using multiple poses, and score results (Months 18-24)*

March 2007 - The program GOLD (Version 3.1.1) from the Cambridge Crystallographic Data Center was used to dock the tyrosine kinase inhibitor candidates (obtained from our UNITY search of databases using the quinazoline pharmacophore model) into the ATP site of ErbB2 for virtual screening. GOLD is an automatic docking program that uses a genetic algorithm for docking flexible ligands into protein binding sites. The three times speed-up was chosen as a Genetic Algorithm Parameter. Chemscore was chosen as the scoring function. The Chemscore parameter file was edited to include a Kinase score function and validated to ensure that it has the power to discriminate between the promising TKI candidates and the unpromising candidates. The docking was repeated five times to avoid the stochastic nature of the docking algorithm. The five docking runs resulted in approximately 100 molecules which will be submitted for tests of activity in prostate cancer cell lines.

February 2008 - Database searches using the tyrphostin pharmacophore of the ZINC database (both leadlike and druglike compounds) have been completed. Nearly 11,000 compounds were identified and virtually screened as described above. Fifty compounds have been identified as promising TKI candidates.

February 2009 – The fifty candidate compounds have been extracted from the ZINC database and sources for obtaining these compounds for testing have been identified.

5. Determine activity and specificity of novel ErbB2-targeting molecules: specifically, the ability of each small molecule to ablate ErbB2 activation (Months 18-36)

February 2008 – One compound has been shown through MTT assays to inhibit the growth of HER2Δ16 cancer cells.

February 2009 – Two compounds have been identified with standard alimar blue assays to inhibit the growth of MCF7 cancer cells.

6. Determine the impact of novel ErbB2-targeting molecules on PC cell growth: specifically, determine the effect of the ErbB2 inhibitor on the growth of LNCaP-ErbB2 cells using several standard cellular growth assays. (Months 18-36)

Plans are unchanged.

7. Deliverables/measurable outcomes: Dr. Stevens will prepare or oversee the following:

a. *Semiannual reports will be submitted to the Co-PI*

Dr. Stevens has submitted semiannual reports to the coPI.

b. *One abstract will be submitted to a professional conference each year (Months 12, 24, 36)*

No off-campus presentations have yet been made by Dr. Stevens. Her generation of computational data and of completed x-ray crystal structures, however, leaves little doubt that significant publishable progress has been made. Unfortunately, Hurricane Katrina interrupted the momentum associated with presenting results at scientific meetings. Being displaced in Virginia from September – December 2006 meant that abstracts planned for the American Crystallographic Association, American Chemical Society, and American Association of Cancer Research could not be submitted.

Dr. Stevens was invited to present a seminar on her research at Towson University (Nov. 2006) as part of their seminar series. She presented a seminar that included results from this research project "Structural Studies of Inhibitors of Cancer Initiation and Growth".

February 2008: Dr. Stevens presented a seminar on January 25, 2008 at the LSU Health Sciences Center that described the results obtained in this research project. The title of the seminar was "Identification of Tyrosine Kinase Inhibitors by Molecular Modeling". A poster was also presented at the national meeting of the American Chemical Society. (Peter Tran, Naijue Zhu, and Cheryl L. Klein Stevens, "X-ray Crystal Structures of

ErbB2 Tyrosine Kinase Inhibitors (TKIs)", 233rd National Meeting of the American Chemical Society, Chicago, March 2007).

February 2009: Dr. Stevens presented an invited paper in the Chemistry in Medicine Symposium at the 235th National Meeting of the American Chemical Society in New Orleans in March 2008 entitled "Searching for New Tyrosine Kinase (TK) Tumor Growth Inhibitors".

In addition, she presented an invited seminar on January 26, 2009 at Colorado State University – Pueblo that described the results obtained in this project. The title of the seminar was "X-ray Crystallographic and Molecular Modeling Studies of Inhibitors of Tumor Growth".

c. *Students involved in the research will present a poster at the annual research workshop (Months 12, 24, 36)*

Dr. Stevens' research student, Nicole Bell, has already presented her work at the American Chemical Society meeting in August 2005. These presentations included the following:

- Nicole M. Bell, Naijue Zhu, and Cheryl L. Klein Stevens, "A Crystallographic Study of ErbB2 Tyrosine Kinase Inhibitors", 230th American Chemical Society National Meeting, Washington, DC, August 2005.

Peter Tran presented a poster at the American Chemical Society meeting in March 2007.

- Peter Tran, Naijue Zhu, and Cheryl L. Klein Stevens, "X-ray Crystal Structures of ErbB2 Tyrosine Kinase Inhibitors (TKIs)", 233rd American Chemical Society National Meeting, Chicago, IL 2007.

A poster was presented at the 237th National Meeting of the American Chemical Society in March 2009.

- Iris Alao, Ryan Graham, and Sean Haron, "Cell Growth Inhibition Studies of Potential Tyrosine Kinase T umor Growth Inhibitors", Salt Lake City, March 2009.

d. *One competitive grant application will be submitted by end of Month 24*

A grant proposal was submitted to the DoD HBCU/MI Partnership Training Award program entitled "Developing a Drug Discovery Program for Combined Breast Cancer Therapy" 03/1/10 – 02/28/14,

e. *One paper will be submitted by end of Month 36*

A manuscript was published as a result of this work. Another is planned for submission in the summer of 2008.

Zhu, N.; Tran, P.; Bell, N.; Klein Stevens, C. L. "Tyrphostin Tumor Growth Inhibitors of EGFR and ErbB2 Tyrosine Kinase", *J. Chemical Crystallography*, 37, 679-683 (2007).

SPECIFIC AIM II
Increase number of Xavier University investigators focused on PC research.

A. **The Co-Project Director will identify two additional Junior Faculty that express an interest in PC research in order to include them in the group activities (Month 1)**

One Xavier University faculty member, Dr. Gurdial Arora of the Department of Mathematics, was partnered in 2005 with Dr. Suresh Sikka, a Tulane Cancer Center prostate cancer researcher. Dr. Arora is using his expertise in statistics to analyze data collected by Dr. Sikka. Xavier students are learning techniques in the Sikka lab while gaining exposure to prostate cancer research. This project has developed as described below.

In August 2007, Dr. KaTani Parker-Johnson was hired in the biology department oat Xavier. Dr. Parker-Johson is the wife of the late Dr. Dunae Johnson. KaTani has a background in cancer genetics and genomics related to health disaparities and along with her husband, is the first wave of faculty at Xavier specifically to build the cancer research programs (CV in Appendix 1, Statement of Research Plans in Appendix 2). She also recived a grant to start her research in summer 2007 at Tulane University and immediately involved one Xavier student (Abstract in Appendix 3). Dr. Parker-Johnson is in the Biology Department were faculty use shared lab space and also have a large teaching load. Dr. parker-Johnson received a start up package fro the Xavier participation in the Louisiana Cancer Research Consortium and immediately started working in her husbands lab and the lab of Dr. Wiese in the College of Pharmacy. With program participant Dr. Ireland as her chair, we expected that Dr. Parker Johnson would receive a light teaching load so she could establish her research. This was not to be the case and in Fall 2007 and

Spring 2008, Dr. Parker-Johnson received one of the largest teaching loads in the Biology Department. Under these conditions, Dr. Parker-Johnson kept her research underway, mentored two Xavier students and took them to the 2008 AACR meeting. Unfortunately, Dr. Parker-Johnson's career in the Xavier Biology Department was cut short when she did not receive a new contract in March 2008. It is not clear the reason for this decision. Recognizing the potential of Dr. Parker-Johnson, the Xavier College of Pharmacy picked her up on a new contract in a non-tenure track position in the college where she will focus on health disparities related cancer research and mentoring students in cancer research. Thus, we are supporting Dr. Parker-Johnson with start up funds from the LCRC and while we orgionally proposed to support her with supply funds from the requested DOD PC program no-cost extension, funds were limited and she was not supported by the XU DOD PC program.

***Title*: Differential Expression of Biomarkers of Prostate Cancer in Africo-American men using Mathematical Models.**

Gurdial Arora, Ph.D. - Xavier University, New Orleans, LA, and
Suresh C. Sikka, Ph.D., HCLD – Tulane University Health Sciences Center, New Orleans,
Brittany Richardson - Xavier University, New Orleans, LA
Asim Abdel-Mageed - – Tulane University Health Sciences Center, New Orleans

Hypothesis: Certain biomarkers are involved in differential expression of selective genes and their mutations that are responsible for onset and progression of prostate cancer in Africo-American men. Some of these mutations are possibly due to altered cellular oxidative stress in the susceptible prostate. We hypothesize that specific mathematical models will help in early stage expression of certain selective biomarkers in Africo-American men that will expand our understanding of pathobiology of development of prostate cancer.

Goals: Our overall goal is to validate such potential biomarkers and/or selective genes (influenced by oxidative stress using), by characterizing them using mathematical models.

Introduction: As men age, environment, diet, and genetics play a significant role in the development of benign prostatic hyperplasia (BPH) or prostate cancer (PC). How these etiologic factors interact in prostate growth and differentiation leading to cancer is not fully known. Altered redox mechanisms affecting cellular oxidative insult leading to specific gene mutations is now considered to be a key hypothesis in this respect. Oxidative insult or stress is a condition caused by increased generation of free radicals and/or decreased antioxidant capacity in associated cells and tissues. By far, the preventative and early therapeutic options available to men prone to BPH and/or PC are limited - mainly due to the lack of markers for early detection of these conditions. In addition, there is no clear understanding of cellular and molecular mechanisms that are responsible for genetic mutations due to altered oxidative stress in the aging prostate.

Specific Aims and Progress:

1) Oxidative stress and prostate growth: Dr. Sikka in his laboratory at Tulane recently demonstrated a differential growth and inhibition pattern in benign and normal prostate epithelial cells in response to oxidative insult. BPH cells, unlike normal prostate cells, showed significant proliferative response over control under very low oxidative stress. By induction of apoptotic stimuli (investigated by caspase activation), this selective BPH proliferation could be prevented by antioxidants (vitamin E and selenium). Dr. Sikka hypothesizes that low chronic oxidative stress is responsible for inducing specific genetic and physiological events in cells that are most prone to such altered responses.

2) Calcium channels as Biomarkers: In this context Dr. Sikka and colleagues have observed that intracellular calcium ($[Ca^{2+}]i$) plays a vital role that may regulate the differential growth patterns that exists between BPH and normal prostate epithelial cells under conditions of induced oxidative stress. The mRNA expression of T-type Ca^{2+} channel was observed only in BPH cells at low oxidative stress (even near the resting membrane potential) resulting in the elevation of basal $[Ca^{2+}]i$ concentration. Dr. Sikka is currently evaluating other specific $[Ca^{2+}]$ channels in normal and cancer cells. In addition, the preliminary results have shown that the expression levels of gene and/or protein of cytochrome c oxidase II and III subunits are extremely low in BPH cells but relatively higher in normal prostate epithelial cells. Since the mitochondrial membrane potential and activities of such key redox enzymes play an important role in activation of caspase cascade leading to induction of apoptosis, we plan

to evaluate the expression of these subunits II, III at both gene and protein levels. Dr. Sikka hypothesizes that this differential response is due to induction of specific mutations and/or deletions in these key mitochondrial enzymes. Evaluation of such mutations/deletions with functional expression of selective calcium channels can be used as biomarkers for early detection and prevention of benign and malignant prostate disease in aging men. In collaboration with Dr. Abdel-Mageed, they plan to specifically use the patient resources (biopsy tissue, EPS and blood samples) from Caucasian and Africo-american men of various age groups and focus on evaluation and differential expression of selective genes responsible for these biomarkers. ***Mathematical Modeling of Biomarkers Expression:*** Dr. Arora's participation related to this project is multifold. He now understands the specific problems (epidemiological, pathophysiological, genetic linking, early diagnosis, prevention and treatment) related to this area and is using his expertise in the area of mathematical modeling and applied bio-statistics to analyze the data so far generated by Dr. Sikka's related research. ***Quantitative or mathematical modeling refers to*** the use of mathematics to construct an equation (or more typically, equations) that can reflect, in quantitative terms, what are considered by the experimentalist or clinician to be the key biological processes and use this as a predictive tool. Considering an increased serum prostate-specific antigen (PSA) level as a quantitative marker of prostate cancer growth,, , Swanson et al [1] constructed a theoretical model and a simple equation that can be written in words as follows:

Rate of Change of Serum PSA = Production of Serum PSA by Malignant Prostate Cells + Production of Serum PSA by Benign Prostate Cells – Loss of Serum PSA from the body

These words can then be translated mathematically into the following differential equation :

$$\frac{dp}{dt} = \beta_h V_h + \beta_c V_c - gamma \text{ pt}$$

where pt, is the serum PSA level at time t; V_h and V_c are the volumes of benign and cancerous PSA producing cells, respectively, and PSA produced by benign and cancer cells at the rates β_h and β_c, respectively.

. Three commonly used methods that are available to us are (a) multivariate models expressed through nomograms, (b) tree-based methods, and (c) artificial neural networks (ANN). These methods attempt to maximize predictive accuracy, do not require a pre specified PSA threshold, and provide a measure of prostate cancer risk that is specifically tailored to each patient based on any set of risk factors.

In a recent problem studied by Robert Nam et al [2] , the authors constructed a clinical nomogram instrument to estimate individual risk for having prostate cancer (PC) for patients undergoing prostate specific antigen (PSA) screening, using all risk factors such as age, family history of PC, ethnicity, urinary voiding symptoms, and free/ total PSA ratio, in addition to PSA and DRE for prostate cancer. In order to develop tools that can accurately predict prostate cancer risk, account for patient heterogeneity as in our Africo-American men, and easily translate the information from bench to bedside, we plan to use such statistical and mathematical modeling techniques for our data. We will develop nomograms based on risk factors associated with prostate cancer for Africo-American population. Dr. Arora is currently using SPSS software and is uploading the data so as to apply statistical and mathematical techniques (such as differential equations) in order to model the problems.

One new Xavier student (Jessica Saucier) is now learning to use the software and relevant statistical and mathematical techniques. The goal is to collaborate with Dr. Sikka's and Dr. Abdel-Mageed's groups on this project, learn from their expertise and plan to submit extra-mural grant in the near future.

Further Progress and Plans: Miss Brittney Richardson gave a presentation on Feb 26, 09 at Xavier University of Louisiana. Her title of presentation was " Differential Expression of biomarkers of Prostate Cancer in African- American using mathematical models. However Miss Richardson was asked not to continue working on this problem due to poor performance after her presentation. However we selected another student in January. Since she is new and did not have background in this area, we are working with her so that she can familiarize with this area. We hope that the student will continue working in this area after she learns software skills also to analyze the date.

We analyzed the data on prostate cancer provided by Dr. Sikka from Tulane University. We looked at pre-psa level, age, race, size of the prostate, and Gleason score of about 120 patients. During our preliminary analysis, we looked at multiple regression analysis techniques and classification and/or regression tree. This approach has several potential advantages. However the results are still preliminary and hopefully we will have some conclusion based on our analysis in near future. Recently it was reported in the literature that a group of researchers from UCSF is working on another prediction model. The group is working on another gene variant to use the clinical data with PSA levels, Gleason score, and tumor staging. The goal is to see that if it improves the accuracy. Dr. Arora has

established the collaboration with Drs. Sikka and Mageed. He along with Brittany, have learnt many biological and cell-culture terminology such as cellular confluency, cell proliferation and toxicity, in vitro & in vivo approaches, apoptosis, cell signaling, etc. as a result of being in these research facilities.

Miss Jessica Saucier, new student, will analyze the data after she becomes familiar with terminology and software skills. At the moment, she is reading the literature to get familiar with the work that has been done.

B. **Establish participation of the selected Junior Faculty in Tulane Cancer Center**
The program PI, Dr. Wiese, is informed of and otherwise identifies cancer research seminars at the Tulane Cancer Center and at other universities in the city (LSU Health Sciences and University of New Orleans). Then, Dr. Wiese uses email to notify faculty involved in the DOD programs at Xavier and set up car pooling to attend. Someone from this group has attended most bi-weekly cancer center seminars and most faculty have attended at least one every few months. Attending these TCC seminars has become a regular event for the Xavier faculty involved in cancer research. The tradition from recent years of alternating the sponsor and location of the cancer seminars between Tulane and LSU Health Sciences continues. Attempts to have Xavier cancer researchers invite speakers in to give seminars At Xavier has not been successful. We have tried to revive this effort with no success. The main obstacle is that the Xavier faculty involved in cancer research are not willing or able to identify a suitable speaker and then the schedules of these faculty and students prevents solid enthusiasm for the idea. Of the Biology, Chemistry and College of Pharmacy at Xavier, only Chemistry has an established seminar time. The chemistry seminars are held on Thursdays at noon, the same time as the LCRC cancer seminars at Tulane and LSU. The Xavier LCRC budget has funds to support seminar speakers and we are planning to use these funds to bring in 2-4 cancer research speakers into the Chemistry seminar series.

C. **Subscribe to cancer- and/or prostate-related journals (Month 1)**
All participants in the program were asked in Y2 of the program what journals they need access to and with recent expansions of the Tulane and Xavier electronic library collections, no deficiencies were identified. It should be noted that the Xavier faculty involved in this project have access to the Tulane library resources which augments the constantly increasing Xavier library collection.

D. **Establish information-flow from the Office of Sponsored Programs about funding opportunities in PC (Month 9)**

Xavier University's Senior Vice President for Resource Development, who heads the university's Office of Sponsored Programs, regularly forwards information about new funding opportunities to the PI, who passes it on as appropriate to the Xavier University researchers. The Xavier Office of sponsored Programs offers information and training sessions each fall regarding the identification of grants, process for application and procedures for processing applications within Xavier. Xavier retains multiple grant consultants for faculty to use to discuss grants ideas, grant development as well as for the purpose of pre-review of grants.

E. **Determine Tulane Cancer Center mentors for the Junior Faculty (Month 6)**
See section II.A. above.

F. **Junior Faculty collect preliminary data (Months 7-24)**
The new research partnership between Drs. Arora of Xavier University and Sikka of the TCC) has developed a budget and account to fund students and purchase supplies and equipment. We expect that Dr. Parker-Johnson will continue to generate preliminary data with support from XU LCRC start up funds.

G. **Host a workshop on grant preparation and how to identify proper funding opportunities (Month 24)**
Xavier faculty involved in this project have been working with their mentors and the Xavier office of Sponsored programs to identify suitable funding opportunities. The program PI has also informed participating faculty about local or regional grant writing workshops. No faculty have yet attended these workshops. It is the opinion of the PI that the faculty in this program are aware of relevant funding opportunities. The key to making use of these involves finding the correct match for the Xavier and Tulane faculty team. This match involves submission schedule related to class schedule as well as research subject area.

H. **Junior Faculty develop grant proposal (Months 25-36)**

Plans are unchanged. Dr. Arora and Sikka submitted a pilot project proposal for the Xavier –Tulane NCI P20 program in 2006. This proposal was not funded due to fact that they wanted to establish a student training program and P20 program as looking for research. The program PI and others involved in the P20 program have worked with Drs. Arora and Sikka to identify an appropriate funding mechanism.

SPECIFIC AIM III
Establish long-term collaborative relationship between Xavier University and Tulane University Cancer Center.

A. **Grant membership in the Tulane Cancer Center to Xavier University researchers including Junior Faculty (Month 1)**
All Xavier faculty involved in this program have either been approved as adjunct faculty at Tulane or this approval is pending. Once approved, this status allows Xavier faculty to be contributing members of the Tulane Cancer Center (TCC) as well as the Louisiana Cancer Research Consortium (LCRC). As, members, these faculty can use the various core facilities at the cancer center at a reduce rate. To date, all Tulane mentors have facilitated the use of any needed cancer center cores with or with out membership. This adjunct status also allows the Xavier faculty doing cancer research to use the Tulane library resources.

B. **Include Xavier University researchers (including Junior Faculty) in the Tulane Cancer Center programs/working groups/task forces, which focus on a particular organ such as the prostate or on a specific class of phenomena such as signal transduction (Months 1, 7)**
All faculty involved in the Xavier DOD Cancer programs are now integrated into the Molecular Signaling focal group of the LCRC. These faculty are exposed to a wide range of cancer research by attending the Molecular Signaling research meetings. In addition, these faculty are now involved in building stronger ties between Xavier and the LCRC. We have established a monthly Cancer Research lunch meeting at Xavier (see III H below).

C. **Include Xavier University researchers (including Junior Faculty) in the Tulane Cancer Center PC journal club (Month 1)**
Tulane no longer has a Prostate cancer journal club. However, Xavier faculty doing cancer research are now included in and can present at the Molecular Signaling research meetings of the LCRC (See section III G below).

D. **Grant access to core research facilities at the Tulane Cancer Center (Month 1)**
Both Drs. Ireland and Stevens share resources in their Tulane mentor's labs. In addition, now that both are members of the TCC and LCRC, they can initiate use of the various cancer center core facilities. These projects have not yet required resources in the LCRC core facilities.

E. **Establish external advisory board (LSU-Tulane Cancer Research Consortium) for the purpose of reviewing program progress, offering solutions to identified problems, and providing an ongoing mechanism for planning improved collaboration (Month 3, 12, 24, 36)**
No formal external advisory board has been established. However, the Xavier faculty doing projects in this program interact closely with their mentors and Dr. Wiese, the program PI interacts weekly with Dr. Steven Hill, Program Director and Dr. Roy Weiner, Director of the Tulane Cancer Center. These meetings have formed a very good working relationship that readily formulates solutions to problems that have come up.

F. **Invite Tulane University researchers to give seminars at Xavier University (Months 3, 7, 15, 19, 27, 31)**
Cancer related seminars at Xavier planned for fall 2005 and Spring 2006 were canceled and have not restarted. We do have the twice monthly cancer research discussion lunch established since 2006 which receives good attendance by XU faculty interested in cancer research as well as collaborating Tulane faculty (see III H below).

G. **Invite Xavier University faculty-at-large to attend seminars related to PC research (Months 3, 7, 15, 19, 27, 31)**
An effort has been made by Dr. Wiese to inform all faculty in the Chemistry and Biology departments as well as all faculty in the College of Pharmacy about cancer related seminars in the city. These faculty are well informed about any cancer research seminars that will take place at Xavier.

It should be noted that Xavier cancer research faculty are informed about and encouraged to attend all the cancer

related seminars and working groups in the LCRC. The LCRC invited speaker series is every other Thursday at noon alternating between Tulane and LSU. Other LCRC discussion groups include: Friday Afternoon Encounters to discuss recent data, the Immunology Club, the Apoptosis and Cell Survival meetings (2x per month) and the weekly Prostate Cancer Group Meetings at LSU; the weekly Breast/Ovarian Group Meeting and the weekly Stem Cells and Cancer Group Meeting at Tulane Cancer Center. The two DOD programs at Xavier have also established a bi-weekly Cancer research Discussion group where faculty involved in DOD projects rotate presenting about the latest status of their project. Tulane mentors and collaborators as well as students are invited to these meetings and this program has been very helpful in bringing our group together. This cancer focused work in progress series has become very popular among faculty interested in cancer research and new faculty hired to do cancer research supported by the LCRC.

H. **Hold annual workshop, open to all in the Xavier University and Tulane communities, for all PC participants to present results of the preceding year. Faculty, students, and staff will attend and at least one person from each group will present a talk; students will present posters (Months 12, 24, 36)**
Our attempts to hold a Cancer Research symposia at Xavier have been foiled by scheduling conflicts with university and department events. We were not able to generate interest in this for 2007. It appears that with all the LCRC seminars, working group meetings, annual retreat and other cancer related discussion meetings, Xavier faculty are not interested in developing a symposia at Xavier. It should be noted that all Xavier students involves in the DOD programs at Xavier present at the universities annual Festival of Scholars in April. In addition, since all Xavier faculty involved in this program are members of the LCRC, they present their work at the annual LCRC retreat each Spring. This event has become the New Orleans area symposia where all cancer researchers from Xavier, Tulane and LSU come together to present and learn from each other.

We have established a monthly Cancer Research lunch meeting at Xavier where the faculty involved in our DOD Cancer programs rotate in giving "work in progress" presentations to the group. These meetings are held on a Monday at noon each month and are well attended by all members of the labs involved and our Tulane mentors-collaborators also attend. These meetings have not only assisted Xavier faculty with their projects, but have also provided a place where we can all se what each other are doing. Other Xavier faculty interested in cancer research are now attending these meetings and we may expand these sessions to twice a month. The schedule for these meetings is listed in Appendix 1.

I. **Report the activities of the PC program to the presidential-level Tulane-Xavier University Partnership Committee (Months 12, 24, 36)**
On September 18, 2006, Dr. Wiese presented a summary and update of all of the Cancer Research programs at Xavier to the university administration, including the president. This type of presentation is now a yearly event at Xavier. Xavier president Dr. Norman Francis has frequently expressed enthusiasm for building cancer research programs at Xavier and he has been a board member of the LCRC for the last two years. The result of this meeting was great enthusiasm from the president to the deans and associate deans to capitalize on existing cancer research programs. Specific areas of interest were obtaining additional funding for research, building cancer related courses and student experiences and hiring faculty with cancer research interest.

With Xavier a member of the LCRC, Dr. Wiese the Associate Director for Xavier, and Xavier President Dr. Norman Francis a member of the LCRC board, Dr. Wiese is in close contact with Dr. Francis as well as senior Tulane administrators about cancer programs at Xavier.

J. **Ad-hoc committee will explore feasibility of academic course on cancer biology or cancer chemistry taught jointly by Xavier University and Tulane faculty (Month 13)**
A new course "Cancer Biology and Health Disparities" has been developed by Dr. Wiese and other Xavier and Tulane faculty involved in the Xavier-Tulane NCI P20 planning grant. This course was held for the first time in Spring 2007, 2008 and 2009 and has become a popular course for Xavier student interested in cancer research or clinical careers. (see Appendix 5 for course schedule).

K. **Submit competitive grant proposal for renewal and expansion of Xavier University-Tulane collaboration in PC (Month 24)**
The Xavier-Tulane NCI P20 Planning grant was submitted in February 2005 and the program started during the Katrina evacuation in October 2005. This program has established 2 additional teams of Xavier-Tulane cancer research pilot projects, a Xavier student training program for cancer research, a Cancer Biology and Health

Disparities course and added health disparities and cultural competence education to the Xavier and Tulane Pharmacy and Medical professional programs. Xavier has now become the third partner in the Louisiana Cancer Research Consortium (LCRC) that includes funds to build broad aspects of the cancer research program at Xavier. Xavier would not have been included in the LCRC without the DOD PC and DOD BC programs having been established. Dr. Stevens, Xavier PI of project #2 in this program organized a group of Xavier and Tulane faculty to submitt a proposal to the DOD in early 2009. This proposal builds completely on the collaborations and science developed in this DOD PC program.

KEY RESEARCH ACCOMPLISHMENTS

· One additional research project was established in the program for a total of three.
· Two faculty with cancer research experience have been recruited at Xavier (one died in Dec 2007).
· Project #1 Demonstrated that the wild-type p53 inhibits NF-κB activation by an average of 40 % in the absence of TNF-alpha, the endogenous NF-κB inducer (Ireland/Abdel-Mageed)
· Project #1 Demonstrated that NF-κB inhibits p53 in PC-3 and DU-145 cells (Ireland/Abdel-Mageed)
· Project #1 Demonstrated that p53 DNA binding motif is required for NF-κB activation of p53 regulated genes in PC cells lacking or expressing mutated p53 gene (Ireland/Abdel-Mageed)
· Project #2, Pharmacophore models have been made to define the structure requirements of ErbB2 inhibitors (Stevens/Jones)
· Project #2, Homology model of ErbB2 has been made and used to identify 50 compounds to be screened for antagonist activity. One manuscript published describing the selection process. (Stevens/Jones)
· Project #2, Two lead compounds have shown significant activity in reducing the proliferation of cancer cells over expressing ErbB2 (Stevens/Jones) in bioassays run at Xavier.
· Project #2, Fifty new lead compounds have been identified using the virtual screening method developed.
· Project #2, A new CoMFA QSAR model was developed for virtual screening that has yet to be validated.
· A Cancer Biology and health Disparities course has been established by the NCI P20 grant that is a "spin off" of this DOD program. This course involves Xavier and Tulane students and faculty and has become very popular after three years of presentation.

REPORTABLE OUTCOMES

· Poster presentations and invited presentations at national meetings
· One manuscripts published, two in preperation.
· A grant proposal was submitted to the DoD HBCU/MI Partnership Training Award program entitled "Developing a Drug Discovery Program for Combined Breast Cancer Therapy" 03/1/10 – 02/28/14,
· Involvement of Xavier students in three research projects
· Program members involved in projects in the Xavier-Tulane NCI P20 planning grant.
· Established a monthly Cancer Research lunch meeting at Xavier.
· Xavier has hired Dr. Duane E. Johnson and KaTani Parker-Johnson, funded cancer researchers that have a focus on health disparities research.

CONCLUSIONS

The prostate cancer research program started in Y1 continues with the addition of one more Xavier-Tulane collaborative pair and the hire of two new African American faculty, one with cancer research funding. This program was severely impacted by Hurricane Katrina in 2005 by loss of supplies and loss of time. However, through the efforts of the program participants, the administrations of both Xavier has recovered and Tulane and now with the award of one additional year of funding from the DOD, this program developed and accomplished most program goals. The two primary research projects in the program are making good progress, presenting their work and preparing manuscripts. The one additional project added in 2005 is now underway and Xavier students are involved in this project. Xavier hired cancer researcher Dr. Duane E. Johnson who brought a cancer research grant to the small group of cancer researchers established by the Xavier DOD programs. Unfortunately, Dr. Johnson died in December 2007. Xavier also hired Dr. KaTani Parker Johnson who is now establishing a cancer research program with focus on health disparities. The 6 Xavier faculty involved in both Xavier DOD programs continue to work closely with each other and administrative support is provided by Dr. Wiese as PI of both programs. A monthly cancer research lunch seminar series has been established for both programs and this has become a central point in communicating about our projects to peers, mentors and collaborators. Some faculty involved in the Xavier DOD programs are also involved in the NCI P20 planning grant awarded to Xavier and Tulane in October 2005. This DOD program lead the way for Xavier to be included in the Louisiana Cancer Research Consortium (LCRC)

which now is supporting the continued development of cancer programs at Xavier by providing start up funds, seed funds and other infrastructure resources needed.

REFERENCES

1. Krsitin Swanson et al, On the Use of Quantitative Modeling to Help Understand Prostate-Specific Antigen Dynamics and Other Medical Problems, American Journal of Clinical Pathology, Volume 199, 2003, 1-4.

2. Robert K. Nam, Assessing Individual Risk for Prostate Cancer, Journal of Clinical Oncology, 2007, V-25, 3582-358

APPENDICES

A-1. Xavier Cancer Research Discussion Lunch Schedule 2008-2009
A-2. Xavier-Tulane Cancer Course Schedule

Appendix 1

Louisiana Cancer Research Consortium

Monday Cancer Research Discussion Meetings at Xavier

Noon – 1:00pm
Room 420 Xavier College of Pharmacy

Lunch provided (11:45am)

Date:	Presenters
Monday September 22, 2008	Student Research Presentations (NCI fellows)
Monday October 6, 2008	Student Research Presentations (4) Stevens Lab
Monday October 20, 2008	Shuh Project: Transcriptional regulation of the serum response pathway by the Human T-cell Lymphotrophic Virus Type I (HTLV-I) Tax protein.
Monday November 3, 2008	Johanson Project: Defining the role of FOXO1a in Pax3-FOXO1 DNA binding
Monday November 17, 2008	Biliran Project: "A potential role of anoikis effector Bit1 (Bcl-2 inhibitor of transcription 1) in tumorigenesis and metastasis"
Monday December 1, 2008	Bhattacharjee Project
Monday January 12, 2009	Wiese-Hill Project
Monday January 26, 2009	Parker-Johnson Project
Monday February 9, 2009	LCRC Gene Therapy/Dr. Wolfgang/Dr. Muniruzzaman
Monday March 2, 2009	Ireland-Mageed Project
Monday March 16, 2009	Foroozesh Project, presented by Dr. Jiawang Liu: "Synthesis of Ceramide Derivatives"
Monday March 30, 2009	Kolesnichenko Project
Monday April 13, 2009	Mandal Project
Monday April 27, 2009	Dr. Wiese, LCRC equipment overview
Monday May 18, 2009	Stevens Project
Monday May 25, 2009	Wang-Burow Project
Monday June 8, 2009	Zhang Project
Monday June 22, 2009	MaGee Project

Appendix 3

Spring 2009 Course Schedule: **Biol 4000, PHCY 4001 Cancer: Causes, Treatment and Disparities**
3 credit hours, Monday and Wednesday 4:00 – 5:15pm, room 1203 Tidewater Building, Tulane Medical Center

Xavier Course Coordinator: Thomas Wiese, Ph.D., Xavier College of Pharmacy Room 309, Phone: 520-7433, E-mail: twiese@xula.edu, Office Hours: M, W, F 2-4 pm or by appointment.

Required Text: CANCER MEDICINE 6, HOLLAND & FREI, EDS. 2003, NCBI BOOKSHELF: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=books , Inside Cancer, from Cold Spring Harbor Press: http://www.insidecancer.org/ , World Cancer Report 2008 from the World Health Organization: http://www.iarc.fr/en/Publications/PDFs-online/World-Cancer-Report AND ADDITIONAL READINGS

Dates	Topic/Activity	Instructor	Chapter, Readings
January 12	Introduction, causes treatments, disparities, and costs of cancer	C. Miller (TU), T. Wiese (XU)	Inside Cancer web site
January 14	Chemical Carcinogenesis	C. Miller (TU)	Ch. 17, WCR: 2.1-4, 2.6, 2.9, 2.13-4, 2.16
January 19	***Martin Luther King Day***		
January 21	Radiation and Cancer	C. Miller (TU)	Ch. 19, 20, WCR: 2.10-2.12
January 26	Infections and Cancer	C. Miller (TU)	Ch. 26
January 28	Viruses and Cancer	J. Ross (XU)	Ch. 22-25 WCR: 5.15
February 2	Oncogenes	J. Ross (XU)	Ch. 6
February 4	Tumor Suppressor genes	G. Morris (TU)	Ch. 7
February 9	Genetic Changes in Cancer	C. Miller (TU)	Ch. 8, WCR: 2.15
February 11	Epigenetics and Cancer	M. Erlich (TU)	Ch. 3, 9
February 16	Hormones and Cancer	T. Wiese (XU)	Ch. 18, WCR: 2.6-7
February 18	Angiogenesis	A. Scandurro (TU)	Ch. 11
Feb. 23-25	***Mardi Gras Break***		
March 2	Tumor Immunology	M. Shuh (XU)	Ch. 12-15
March 4	Apoptosis	C. Miller (TU)	Ch. 4, WCR: 3.4
March 9	Invasion and Metastasis	K. Parker-Johnson (XU)	Ch. 10, WCR: 3.5
March 11	***Exam I***	Miller (TU), Wiese (XU)	
March 16	Anti-neoplastic drugs	T. Wiese (XU)	Ch. 44-60, 63-69 WCR: 1.5
March 18	Biological Therapy	H. Safah (TU)	Ch. 55-60, 67-69
March 23-25	***Spring Break Week Tulane (no class)***		
March 30	Systemic Therapy	R. Weiner (TU)	Ch. 44-60, 63-66 WCR: 1.5
April 1	Surgery	TBA (TU)	Ch. 38, WCR: 1.6
April 6	Radiation Therapy	E. Zakris (TU)	Ch. 39, WCR: 1.11
April 8	Pain Management	M. Kahn (TU)	Ch. 77-78, WCR: 1.8
April 13	***Easter Break Tulane (No Class)***		
April 15	Cancer support/Survivor	Pearman	WCR: 1.9, 1.10
April 20	End of Life Issues	M. Gstohl (XU)	Ch. 70, WCR:1.9, 1.10
April 22	Social/Psychological issues for patients & family	C. Faircloth (XU)	Ch. 70-71 WCR: 1.9, 1.10
April 27	Cultural & Diversity issues of cancer/class dinner	M. Lichtveld (TU)	Ch. 34 (outcomes)
TBA	**Comprehensive Final Exam**	Miller (TU), Wiese (XU)	

Course Assignments and Contributions to Course Grade

One mid-term exam (50% course grade) and One comprehensive final exam (50% course grade). Exams will be multiple choice with some short answer component. All exam questions will be made by and graded by the Xavier and Tulane course coordinators Dr. Wiese and Dr. Miller who will attend all lectures in the course. Exams may be administered at both Tulane and Xavier.

Examination schedule

Exam I: March 11th covers: Jan. 12th – March 11th; 14 lectures; 50% of course grade
Final Exam: date, time and location TBA; cumulative from Jan. 12th to April 27th; 50% course grade.

Communication and Electronic Resources

Blackboard will be used for posting course info and material. Your **Xavier email** will be used for email announcements as well as to send updated course grades after each assignment. Thus, **you must check your XU email** or have it forwarded to another email to get emailed information. **The course syllabus is available on the course blackboard page.**