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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.						
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4th Annual Report on Grant #W81XWH-04-1-0252

March 1, 2007 through February 28, 2008

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"

1. Search for a replacement technician to assist in project (Months 1- 4)

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. Identify new student(s) to assist in project (Month 3)

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. Establish a connection between androgen-receptor presence and activity, and drug resistance (Months 1-9)

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-κB 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 IκB 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-κB 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-κB-induced expression of anti-apoptotic proteins (Months 16-21)*

5. Test if chemoresistance is mediated via crosstalk between NF-κB 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 IκB 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-κB (Months 22-27)*

b. *Test p53 level and activity after activating NF-κB. (Months 28-30)*

c. *Test if changes in NF-κB 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”

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.

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.

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'-dihydroxybenzylidencyanoacetyl)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.

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.

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

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 tyrophostin 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.

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 HER2 Δ 16 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).

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.

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*

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. “Tyrophostin Tumor Growth Inhibitors of EGFR and ErbB2 Tyrosine Kinase”, *J. Chemical Crystallography*, **37**, 679-683 (2007).

Plans beyond Feb 2008 - The bioassay portion of this project has been done in the lab of Dr. Frank Jones, Biochemistry, Tulane School of Medicine. In December 2007, Dr. Jones accepted a new position at the Colorado Cancer Center in Denver and left Tulane in January 2008. Dr. Stevens has maintained contact with Dr. Jones and he plans to continue assisting her with the characterization of lead compounds identified in modeling aspect of this project. Plans are for Dr. Stevens to have two students run

cytotoxicity assays on each of the 50 lead compounds in the Wiese Lab at Xavier using the HER2 Δ 16 cancer cells provided by Dr. Jones as well as at least one other prostate cell line (LNCAP). Dr. Wiese has experience with proliferation and cytotoxicity assays in cancer cells and his laboratory is equipped with cell culture facilities and the instrumentation required for Alamar Blue assays. The process of obtaining and testing the 50 target compounds is expected to take at least 6 months. Each compound will be tested at least 4 concentrations in 96 well format in quadruplicate wells in at least three different experiments. Data will be pooled and IC50s determined. Compounds that have been shown to have cytotoxic activity will then be tested in the Jones lab for specific ErbB2 inhibitor activity. Any active leads found in this phase will be reported in a manuscript and used as the basis for a grant proposal to further characterize and optimize the compounds.

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 January 2007, Dr. Duane E. Johnson was hired in the Division of Basic Pharmaceutical Sciences in the Xavier College of Pharmacy. Dr. Johnson was previously a professor at Dillard University in New Orleans and lost his job with Katrina related downsizing. When Xavier Pharmacy advertised for a pharmacology position in Fall 2006, Dr. Johnson applied. One of the key aspects to developing his interest in Xavier was the Cancer Research programs at Xavier, specifically the chance to join one of the DOD programs. Dr. Johnson brought with him a Komen Foundation cancer research grant and was eager to further develop this and other health disparities related projects at Xavier. The CV and Research interests statement from Dr. Johnson are in Appendix 2 of the programs Y3 progress report. We were excited about Dr. Johnson joining our cancer research group at Xavier. In the first half of 2007, Dr. Johnson established his lab at Xavier and also participated in teaching course sin the spring and summer sessions. In summer and fall 2007, Dr. Johnson took medical leave for ophthalmic surgery and started teaching and research late in the fall semester. Unfortunately, Dr. Johnson died suddenly Dec 4, 2007 due to complications related to diabetes. This event has been quiet upsetting for many of us that got to know Duane Johnson and it certainly has reduced the growth of our small cancer research program. Dr. Johnson died before he was able to build newly established collaborations at Xavier into research manuscripts and grant proposals.

In August 2007, Dr. KaTani Parker-Johnson was hired in the biology department oat Xavier. Dr. Parker-Johnson is the wife of the late Dr. Dunae Johnson. KaTani has a background in cancer genetics and genomics related to health disparities 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 received 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 here 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 form the LCRC and propose to support her with supply funds from the requested DOD PC program no-cost extension. She has also taken over her

late husbands Komen grant which goes through 2008. We expect that Dr. Parker-Johnson will be making application for external funding this next year.

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

**Gurdiar 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 aging prostate. We hypothesize that specific mathematical models will help in expression of such selective biomarkers and our understanding of pathobiology of development of prostate cancer in early stage in Africo-American men.

Goals: Our overall goal is to identify such potential biomarkers and selective genes influenced by oxidative stress using *in vivo* and *in vitro* approaches, and characterize them by 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 :

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

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 Xavier student (Brittany Richardson) is also 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: 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.

An NCI P20 Cancer Research and Education Planning Grant under DOD Cancer Training Partnership Grants was submitted for Tulane-Xavier Cancer initiative based upon such collaboration. This competitive grant obtained good recommendation but was not funded. Nevertheless, it is a great opportunity to advance our student's training skills and venture into a long standing collaboration between the two institutions

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. Xavier cancer research faculty were included as attendees in the Tulane Cancer Center Mauvernay Research Excellence Award Seminar & Poster session held in November 2007.

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 this program and the 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 4 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.

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 involved in the DOD programs at Xavier present at the universities annual Festival of Scholars in April.

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 see 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 4.

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.

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 and included Xavier as well as Tulane students (9) and Xavier and Tulane faculty instructors (18). The course was presented again in Spring 2007 with 30 Xavier students involved (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.

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- κ B activation by an average of 40 % in the absence of TNF-alpha, the endogenous NF- κ B inducer (Ireland/Abdel-Mageed)
- Project #1 Demonstrated that NF- κ B inhibits p53 in PC-3 and DU-145 cells (Ireland/Abdel-Mageed)
- Project #1 Demonstrated that p53 DNA binding motif is required for NF- κ B 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, One lead compound has shown significant activity in reducing the proliferation of cancer cells over expressing ErbB2 (Stevens/Jones)
- 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.

REPORTABLE OUTCOMES

- 2 Poster presentations at national meetings and one manuscript published.
- Involvement of 4 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.

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APPENDICES

- A-1. CV of Dr. KaTani Parker-Johnson
- A-2. Research Statement of Dr. KaTani Parker-Johnson
- A-3. Summer 2007 Project of Dr. KaTani Parker-Johnson
- A-4. Xavier Cancer Research Discussion Lunch Schedule 2007-2008
- A-5. Xavier-Tulane Cancer Course Schedule

Appendix 1

Curriculum Vitae

Personal Data:

Name: **KiTani A. Parker-Johnson, Ph.D.**

Citizenship: United States

Address: Xavier University of Louisiana
Department of Biology
1 Drexel Drive
New Orleans, LA 70125
kparker1@xula.edu

Education:

2002-2004 Postdoctoral Fellow, LSU Health Sciences Center, New Orleans, LA
1999-2003 Ph.D., Cell & Molecular Biology, Clark Atlanta University, Atlanta, GA
1995-1997 M.S., Biochemistry, Tennessee State University, Nashville, TN
1987-1991 B.A., Biology, Fisk University, Nashville, TN

Employment:

8/07-present Assistant Professor, Xavier University of Louisiana (tenure track). Responsibilities include teaching general biology and conducting research in breast and prostate cancer to identify novel biological targets for drug intervention.

8/06-7/07 Assistant Professor, University of Nebraska, Omaha (tenure track). Responsibilities included teaching molecular biology of the cell, genetics, and conducting research in breast and prostate cancer to identify novel biological targets for drug intervention.

1/06-8/06 Visiting Assistant Professor, University of Nebraska Medical Center. Conducted research in the area of health disparities in breast cancer in African American women; conducted biological screenings and evaluated cell lines for specific protein expressions.

8/04-12/05 Assistant Professor, Dillard University (tenure track). Responsibilities include teaching (histology, cellular & molecular biology, general biology, and research methodology) to undergraduate students; conducting breast and prostate cancer research on a collaborative project at LSUHSC evaluating the molecular mechanisms associated with genes that are differentially expressed in prostate cancer derived from African-Americans vs other ethnic backgrounds (health disparities research), and serving on committees (pre-dental committee, HBCU-UPS research development group), and the development of new introduction to bioinformatics.

5/03-7/04 Postdoctoral Fellow, LSU Health Sciences Center. Projects include using several software packages for the microarray analysis of genes differentially expressed in prostate cancer cell lines post-infection with adenovirus containing p27, the design and execution of synergistic experiments combining gene therapy and drug therapy, and examining microarray data to evaluate the genes differentially expressed as prostate cancer transitions from androgen dependence to androgen independence.

- 6/03-8/03** **Instructor, Dillard University.** Lectured general biology to pre-freshmen preparing for careers in the natural sciences and public health.
- 9/02-4/03** **Research Associate III, LSU Health Sciences Center.** Responsible for the design and execution of specific experiments on a prostate cancer project to include microarrays, RT-PCR, real-time PCR, evaluation of xenografts, and synergism experiments with novel anticancer agents plus an adenovirus for the delivery of the p27 gene.
- 9/02-5/04** **Adjunct Professor, Dillard University.** Provide instruction in Cellular and Molecular Biology lecture and the laboratory; also taught an independent research course to introduce students to cutting-edge research techniques and General Biology course (lab and lecture) to freshmen.
- 6/01-7/01** **Mentor, Morehouse College, E. E. Just Summer Science Program.** Mentored students in scientific experimental techniques and theory.
- 6/00-8/00** **Instructor, Morehouse College.** Taught Biological Sciences to undergraduate and high school students in the TRIO Summer Program.
- 6/00-8/00** **Instructor, Morehouse College.** Taught a project-based laboratory to pre-freshmen for the Packard Scholars Program.
- 6/99-8/99** **Instructor, Morehouse College, HCOP (Health Careers Opportunities Program).** Taught molecular, tissue culture, and recombinant technology techniques to Pre-Freshmen.
- 6/99-8/99** **Instructor, Morehouse College, IMHOTEP.** Taught molecular biology, tissue culture, and recombinant technology techniques to Public Health students and mentored them during their matriculation through the program.
- 01/99-12/99** **Research Scientist, Morehouse College.** Performed *in vitro* biological assays using novel anticancer agents against various human breast and prostate cancer cell lines.
- 9/99-4/03** **Graduate Student, Clark Atlanta University;** Prospectus research evaluated the genetic changes in prostate cancer cell lines exposed to novel anticancer agents using microarray technology.
- 09/99-12/99** **Teaching Assistant, Clark Atlanta University;** Taught laboratories to undergraduate students to complement lecture series in Biological Sciences.
- 09/98-09/99** **Research Biologist, Morris Brown College.** Performed *in vitro* screening of biological assays for anticancer agents, taught and trained students various tissue culture and molecular techniques.
- 09/97- 6/98** **High School Science Teacher, Northwest High School.** Taught biological sciences to advanced 9th graders.
- 01/97-05/97** **Saturday Scientist Coordinator, Meharry Medical College/Nashville Chapter of The Links, Inc.** Coordinated and conducted experimental laboratory sessions for area high school students to expose them to the latest animal and recombinant DNA scientific technology.

- 06/96-07/96** **Instructor, Meharry Medical College.** Taught Molecular Biology Course for High School students in the *Research Center of Excellence*.
- 08/95-5/97** **Graduate Student, Tennessee State University,** Thesis; *Effects of Phenylacetic Acid Halides on Apoptosis in MCF-7 cells*. Skills acquired in thesis include- dose-response curves, DNA isolation techniques, cell culture of human breast cancer cells (MCF-7, MDA-MB231, MCF-10).
- 09/92-09/95** **Research Assistant II, Meharry Medical College.**
Performed animal studies, tissue culture experiments using bacterial and mammalian cell lines, and molecular biological evaluations using Northern, Southern, and Western techniques.
- 8/90-5/91** **Student Researcher, Fisk University,** NASA Project; Performed assays to determine the best growing conditions of specific strains of algae using HPLC and other methods of chromatography.
- 6/90-8/90** **Student Participant, University of California, Santa Barbara,** Summer Research Academic Institute (SARI); Performed research evaluating the effects of a novel steroidal agent and its role initiating thermogenesis in the genetically obese Zucker rat.
- 6/89-8/89** **East Tennessee State University, Preprofessional Enrichment Program (PREP);** attended MCAT intensive courses such as organic chemistry, anatomy and physiology, and cell biology.
- 6/88-8/88** **East Tennessee State University, Preprofessional Enrichment Program (PREP);** attended MCAT intensive courses such as physics, general chemistry, English, and biological sciences.

Professional Memberships:

- 99-present** Member, American Association for Cancer Research
00-present Member, American Society for Cell Biology
06-present Member, American Association of University Professor

Professional Certifications/Training:

- 2006** National Center for Biotechnology Information (NCBI/NIH) Workshop
2005 National Center for Biotechnology Information (NCBI/NIH) Workshop
2003 GeneSpring Software Training, Levels I and II, Silicon Genetics.
2003 HIPPA Certification

Honors & Awards:

- 2006 American Association for Cancer Research Minority Serving Institution Award for Cancer Research
 2005 Dillard University Faculty Development Award
 2003 American Society for Cell Biology Travel Award
 2003 GlaxoSmithKline Science Achievement Award
 2002 GlaxoSmithKline Science Achievement Award

2001 American Association for Cancer Research Travel Award
2000 American Society for Cell Biology Travel Award
2000 American Association for Cancer Research Travel Award
2000 1st Place Edith T. Biggers Excellence in Scientific Research Award, CAU
2000 Acres of Diamonds Minority Researcher in Training Award
1999 MBRS/RISE Fellowship
1998 Teacher Scientific Merit Award, Northwest High School
95-97 Tennessee State University/Meharry Medical College Bridge Fellowship
87-90 Fisk University Academic Scholarship

Other:

2006 Patent Pending

Presentations and Publications:

Novel DJ56 Causes Tumor Reduction in ER+ Breast Cancer Cells. **K. Parker-Johnson**, B. Knowles, , E. Minnard, N.L. Emmett, D.E. Johnson, **37th Annual San Antonio Breast Cancer Conference, December 2005.**

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DJ52 Proves to Be More Potent Than Tamoxifen against Human Breast Cancer Cell Line MCF-7. Bobby O. Guillory, KiTani Parker-Johnson, David B. Cooke, Duane E. Johnson. *Proceedings for the San Antonio Breast Cancer Symposium (SABCS), Volume 78, December 1999.*

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Appendix 2

An Evaluation of Novel Agents on Potential Biomarker Expression in Prostate Cancer

KiTani Parker-Johnson, Ph.D.

Significance. According the American Cancer Society, in 2007, 234,460 men will be diagnosed with prostate cancer (1). There is always a need for novel anticancer agents because of a phenomenon called multidrug resistance (MDR), which is when a certain cancer no longer responses to a specific treatment. Studies have demonstrated that when breast or prostate cancer reaches Stages III or IV, the disease has become hormone refractory (HR). The first line of anticancer agents eventually lose their ability to inhibit the growth of cancer cells and this often results in metastasis and poor prognosis. Consequently, there is always a need for new antineoplastic agents that have different biological targets, ie estrogen receptor, androgen receptor, and specific growth factors. *Specifically, the novel anticancer agents that will be used for this project have been targeted to the EGF receptor and it is hypothesized that these agents will have significant antiproliferative activity in the prostate cancer cell line models selected. The experiments performed will include current chemotherapeutic agent finasteride as a control.*

Description of the Proposed Project

The objective of this project is prostate cancer cell lines with specific commercially available chemotherapeutic agents compared to a series of novel anticancer agents. This will generate samples to be further analyzed using various molecular biology techniques such as RT-PCR, and Western blotting to evaluate RNA and protein expression levels, respectively.

Specific Aims

The objectives of this study are to demonstrate that the protein and/or RNA levels (this may NOT be a specific correlation) have changed in their expressions due to treatment with the novel agents. *The hypothesis of this project is that there will be a significant decrease in the protein levels of COX-2 and EGFR in treated vs untreated breast and prostate cancer cell lines.* It has been documented that there are isoforms of both EGFR and COX-2, therefore, the objectives are: 1) to evaluate the response of different breast and prostate cancer cell lines to the novel DJ compounds, and 2) to evaluate EGFR and COX-2 expression levels of both RNA and protein.

Methodology and work plan. The human breast and prostate cancer cell lines will be grown in culture using aseptic techniques and treated with a variety of commercially available chemotherapeutic agents and novel anticancer agents in physiological concentrations. The cell line(s) with the best response and lowest concentration of drug will be treated for protein and RNA isolation to measure the expression profiles of genes associated with breast or prostate cancer, respectively. The best response is indicated by the IC_{50} , or inhibitory concentration of 50% of the treated cells. The protein samples will be used in Western blotting assays and the RNA sample will be used in RT-PCR assays. *Preliminary studies suggest that the DJ compounds will have an IC_{50} of $10^{-6}M$, which is the physiologically accepted concentration of most drugs administered. These in vitro data will provide enough support to expand this project to include in vivo experimentation.*

Appendix 3

A Comparative Evaluation of the Growth Inhibitory Activity of Antineoplastic Agents against Novel Human Breast Cancer Cell Line Clone MCF-7-E3

Candace L. Douglas¹, KiTani Parker-Johnson^{1,2}, Thomas E. Wiese³, Duane E. Johnson.³

¹Xavier University of Louisiana, Department of Biology, New Orleans, LA; ²University of Nebraska, Omaha, Department of Biology, Omaha, NE; ³Xavier University College of Pharmacy, Division of Basic Sciences.

Cancer cell line models that demonstrate disease progression from the same donor provide useful insight on pharmaceutical intervention for drug targeting for heterogeneous populations of cells; it is well documented that most tumors are comprised of multiple populations of cancer cells. Therefore, our laboratory used the novel single cell clone E3 from the parental metastatic breast cancer cell line MCF-7 to evaluate the pharmacological response of FDA approved chemotherapeutic drugs. The alamar blue dye exclusion assay method was used to determine the antiproliferation caused by these commercially available chemotherapeutic agents in concentrations ranging from 1 millimolar to 1 nanomolar. The data indicated that there was a dose-dependent decrease in proliferation by chalcone, raloxifene, and tamoxifen after 48 hours of treatment in the E3 cells. Cisplatin and taxol both indicated significant growth inhibition at the millimolar concentration with 38% and 30% growth, respectively. These data provide useful insight on how to potentially provide alternative treatments to subpopulations of metastatic breast cancer cells that express high levels of the estrogen receptor and are sensitive to estrogen or cells that may become refractory to antiestrogens. Specifically, cisplatin and taxol may be alternative pharmacological approaches to treating breast cancers that exhibit tumors with subpopulations that have cells with high densities of the estrogen receptor.

Appendix 4

Louisiana Cancer Research Consortium

Cancer Research Discussion Meetings

Noon – 1:00pm

Room 420 College of Pharmacy

Monthly Research Meeting Schedule

Last Monday of the Month – Lunch provided (11:45am)

Date:	Presenters
Monday October 29, 2007	Stevens-Jones Project DOD PC Project
Monday November 12, 2007	Foroozesh Project LCRC Seed Project
Monday November 26, 2007	Wang-Burow Project DOD BC Project
Monday December 10, 2007	Wolfgang-Miller Project DOD BC Project
Monday December 31, 2007	New Year's Eve – NO MEETING
Monday January 14, 2008	Ireland-Mageed DOD BC Project - CANCELLED
Monday January 28, 2008	Kolesnichenko Project
Monday February 11, 2008	canceled
Monday February 25, 2008	Cancelled due to LCRC Retreat
Monday March 3, 2008	Arora-Sikka Project DOD PC Project
Monday March 10, 2008	Parker-Johnson Project LCRC Start Up Project
Monday March 24, 2008	Zhang Project LCRC Start Up Project
Monday April 14, 2008	MaGee Project LCRC Start Up Project
Monday April 28, 2008	Ireland-Mageed P20 Project - CANCELLED
Monday May 12, 2008	Wiese-Hill DOD BC Project
Monday May 26, 2008	Ireland-Mageed DOD PC Project

Appendix 5

Spring 2008 Course Schedule: Biol 4000, PHCY 4001 Cancer: Causes, Treatment and Disparities
3 credit hours, Monday and Wednesday 4:00 – 5:15pm, room 1204 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, (see <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=books>), Inside Cancer, from Cold Spring Harbor Press: <http://www.insidecancer.org/> AND ADDITIONAL READINGS

<u>Dates</u>	<u>Topic/Activity</u>	<u>Instructor</u>	<u>Chapter,</u>
Readings			
January 14	Introduction, causes treatments, disparities, and costs of cancer	C. Miller (TU), T. Wiese (XU)	1
January 16	Chemical Carcinogenesis	C. Miller (TU)	17
January 21	Martin Luther Kind Day		
January 23	Radiation	C. Miller (TU)	19, 20
January 28	Viruses and Cancer	R. Garry (TU)	22-25
January 30	Oncogenes	J. Ross (XU)	6
Feb. 4-5	Mardi Gras Break		
February 11	Tumor Suppressors	G. Morris (TU)	7
February 13	Genetic Changes in Cancer	C. Miller (TU)	8
February 18	Epigenetics	M. Erlich (TU)	3, 9
February 20	Hormones and Cancer	C. Williams (TU)	18
February 25	Bacterial and Parasitic infections	A. Scandurro (TU)	26
February 27	Invasion & Metastasis	R. Saunders (XU)	10
March 3	Angiogenesis	A. Scandurro (TU)	11
March 5	Apoptosis	M. Burow (TU)	4
March 10	Tumor Immunology	B. Barnett (TU)	12-15
March 13	Presentations by Graduate Students	C. Miller (TU)	HANDOUT
March 16-23	Spring Break Week		
March 24	Exam I	C. Miller (TU), T. Wiese (XU)	
March 26	Intro to anti-neoplastic agents	T. Wiese (XU)	44-60, 63-69
March 31	Systemic Therapy	R. Weiner (TU)	44-54, 63-66
April 2	Radiation Therapy	E. Zakris (TU)	39
April 7	Surgery	M. Wright (TU)	38
April 9	Biological Therapy	B. Barnett (TU)	55-60, 67-69
April 14	Palliative Care/Pain Management	M. Kahn (TU)	77-78
April 16	Assessment of Clinical Trials	F. Mather (TU)	32-34
April 21	Presentations by Graduate Students	C. Miller (TU)	HANDOUT
April 23	End of Life Issues	M. Gstohl (XU)	70
April 28	Social/Psychological issues for survivors	C. Faircloth (XU)	70-71
April 30	Cultural & Diversity issues of cancer	M. Lichtveld (TU)	34
TBA	Comprehensive Final Exam	C. Miller (TU), T. 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 small 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.

Examination schedule

Exam I: March 24th covers: Jan. 14th – March 10th; 17 lectures; 50% of course grade

Final Exam: date, time and location TBA; cumulative from Jan. 14th to April 30th; 50% course grade.

Communication and Electronic Resources

Blackboard will be used for posting announcements, course and lecture material, assignments, surveys, etc. 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. Instructions on how to forward your XU email to another address are posted on the course Blackboard page. **The course syllabus is available on the course blackboard page.**