

AWARD NUMBER:
W81XWH-09-1-0157

TITLE:
Collaborative Undergraduate HBCU Student Summer Prostate Cancer Training Program

PRINCIPAL INVESTIGATOR:
Marvella E. Ford, PhD

CONTRACTING ORGANIZATION:
The Medical University of South Carolina
Charleston, South Carolina 29425

REPORT DATE:
March 2011

TYPE OF REPORT:
Annual Summary

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT:

☒ Approved for public release; distribution unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.					
1. REPORT DATE 31-MAR-2011		2. REPORT TYPE Annual Summary		3. DATES COVERED 1 Mar 2010 - 28 Feb 2011	
4. TITLE AND SUBTITLE Collaborative Undergraduate HBCU Student Summer Prostate Cancer Training Program				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH-09-1-0157	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Marvella E. Ford, PhD Email: fordmar@musc.edu				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) The Medical University of South Carolina Charleston, South Carolina 29425				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT See Next Page					
15. SUBJECT TERMS Prostate Cancer Research Training Program Summer Undergraduate Research Program (SURP) Student Fellows from Historically Black Colleges and Universities (HBCUs)					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	146	19b. TELEPHONE NUMBER (include area code)

14. ABSTRACT

Background: There is a critical need to increase the number of racially and ethnically diverse prostate cancer researchers. The purpose of this 3-year project is to develop a prostate cancer research training program at the Medical University of South Carolina (MUSC) with 12 students from the following three Historically Black Colleges and Universities (HBCUs) in South Carolina: Claflin University, South Carolina State University (SCSU), and Voorhees College. Students from the 3 HBCUs (defined as “Student Fellows”) will participate in research internships in the laboratories/research units of senior prostate cancer research scientists at MUSC. **Specific Aims:** Aim 1.) To provide training in the basics of research design and methods to 4 Student Fellows each year through participation in the MUSC Summer Undergraduate Research Program (SURP); Aim 2.) To immerse 4 Student Fellows each year in a prostate cancer research training curriculum. **Results:** During the current reporting period, 4 Student Fellows were identified, recruited to participate in the program, and admitted to the DOD Collaborative Undergraduate HBCU Student Summer Prostate Cancer Training Program. The Student Fellows were matched with Research Mentors at MUSC, with whom they conducted research in the summer of 2010. Each Student Fellow prepared scientific papers, presented scientific presentations at the end of the summer program, and completed an 8-week Kaplan Graduate Record Examination Test Preparation Course at a local Kaplan Center. **Conclusions:** In the summer of 2010, we provided state-of-the art comprehensive prostate cancer research education and training opportunities for 4 Student Fellows from HBCUs in South Carolina. Each Student Fellow prepared a scientific paper and gave at least 1 scientific presentation. In addition, 1 Student Fellow was selected to give an oral presentation of her summer research project during MUSC’s Annual Perry V. Halushka MUSC Student Research Day on November 5, 2010. Importantly, all 4 Student Fellows from 2010 plus an additional 2 Student Fellows from 2009 had abstracts accepted for poster presentation at the DOD-sponsored national Innovative Minds in Prostate Cancer Today (IMPACT) Conference. An abstract describing the overall program was also accepted for poster presentation at the conference. We are developing a cadre of scientists who are well-prepared to conduct research spanning the continuum from basic science to clinical science to population-based research. The 2011 application process is ongoing, and four Student Fellows will be selected to participate in the Training Program during the Summer of 2011.

Table of Contents

	<u>Page</u>
Introduction.....	
Body.....	
Key Research Accomplishments.....	
Reportable Outcomes.....	
Conclusion.....	
References.....	
Appendices A-G.....	

INTRODUCTION

The Scientific Context of the Training Program

The overarching goal of the Training Program is to recruit the next generation of prostate cancer researchers by exposing undergraduate students (“Student Fellows”) from Claflin University (CU), South Carolina State University (SCSU), and Voorhees College (VC) to prostate cancer research at the Medical University of South Carolina (MUSC), and training them to meaningfully participate in such research activities. **Basic science and clinical researchers** are needed to aggressively pursue and test better methods to decode the prostate cancer fingerprints, which hold the key to understanding the relationship between gene expression and future prognosis. **Population science researchers** are needed who will identify barriers and facilitators of prostate cancer early detection and treatment, and develop strategies to overcome them. The Training Program will provide a pipeline for future generations of these prostate cancer researchers.

The two Specific Aims are to:

Aim 1: Provide training in the basics of research design and methods to 4 Student Fellows each year through participation in the MUSC Summer Undergraduate Research Program (SURP).

Aim 2: Immerse 4 Student Fellows each year in a prostate cancer research training curriculum.

Program Director and Training Team

Dr. Marvella E. Ford is the Program Director. Drs. Rebecca Bullard- Dillard (CU), Judith Salley (SCSU), and Leroy Davis (VC) are Associate Directors. This four-person leadership team collaborates closely in the management and administration of the award, as well as the continued development and enhancement of the Training Program. The Program Director and Associate Directors share scientific interests in health disparities, serve in other leadership roles within their institutions, and meet frequently, both formally and informally. These individuals form the Executive Committee for the Training Program. Each institution has appointed Faculty Advisors consisting of Dr. Kamal Chowdhury (CU), Dr. James B. Stukes (SCSU), and Ms. Gayle Tyler Stukes (VC).

BODY

Statement of Work

Task 1. Identify and Recruit the Student Fellows

- (a) Identify the pool of potential Student Fellows (Year 1, months 1-3; Year 2, months 1-3; Year 3, months 1-3)
- (b) Interview the potential Student Fellows (Year 1, months 1-3; Year 2, months 1-3; Year 3, months 1-3)
- (c) Select the top Student Fellows (Year 1, months 1-3; Year 2, months 1-3; Year 3, months 1-3)
- (d) Match the Student Fellows with Their Research Mentors at MUSC (Year 1, months 1-3; Year 2, months 1-3; Year 3, months 1-3)
- (e) Hold the Kickoff Intensive and Luncheon (Year 1, months 4-6; Year 2, months 4-6; Year 3, months 4-6)

Task 2. Provide Training in Biomedical and Prostate Cancer Research

- (a) Conduct Aim 1: Training in the Basics of Research Design and Methods through participation in the MUSC Summer Undergraduate Research Program (Year 1, months 6-8; Year 2, months 6-8; Year 3, months 6-8)
- (b) Conduct Aim 2: Prostate Cancer Research Training (Year 1, months 6-8; Year 2, months 6-8; Year 3, months 6-8)
- (c) Sponsor the Student Fellows' Participation in a Graduate Record Examination (GRE) course (Year 1, months 6-8; Year 2, months 6-8; Year 3, months 6-8)

Task 3. Prepare Tangible Scientific Products

- (a) Prepare and present scientific abstracts based on the Student Fellows' prostate cancer research (Year 1, months 10-12, Year 2, months 1-12, Year 3, months 1-12)
- (b) Prepare manuscripts that will be submitted to peer-reviewed journals (Year 1, months 10-12, Year 2, months 1-12, Year 3, months 1-12)

Task 4. Evaluate the Training Program

- (a) Assess the number of applicants to the Training Program (Year 1, months 1-4, Year 2, months 1-4, Year 3, months 1-4)
- (b) Assess the number of Student Fellows who apply to graduate school (Year 2, months 1-12, Year 3, months 1-12)
- (c) Assess the number of Student Fellows who are admitted to graduate school (Year 2, months 1-12, Year 3, months 1-12)
- (d) Assess the number of graduate schools to which Student Fellows are admitted (Year 2, months 1-12, Year 3, months 1-12)
- (e) Identify the number of scientific abstracts presented and peer-reviewed publications that result (Year 1, months 10-12, Year 2, months 1-12, Year 3, months 1-12)

KEY RESEARCH ACCOMPLISHMENTS

Task 1. Identify and Recruit the Student Fellows

- (a) Identify the pool of potential Student Fellows (Year 1, months 1-3; Year 2, months 1-3; Year 3, months 1-3)**
- (b) Interview the potential Student Fellows (Year 1, months 1-3; Year 2, months 1-3; Year 3, months 1-3)**
- (c) Select the top Student Fellows (Year 1, months 1-3; Year 2, months 1-3; Year 3, months 1-3)**

To accomplish Tasks 1(a) – 1(c), Dr. Ford, the Program Director worked with Associate Directors Dr. Rebecca Bullard-Dillard (Claflin University), Dr. Judith Salley (SC State University), and Dr. Leroy Davis (Voorhees College) as well as Faculty Advisors Dr. Kamal Chowdhury (Claflin University), Dr. James Stukes (SC State University), and Ms. Gayle Stukes (Voorhees College) to identify potential Student Fellows. The Associate Directors and Faculty Advisors issued a call for applicants to their student bodies and personally approached students whom they felt would be outstanding applicants for the summer research program.

Drs. Ford (Principal Investigator), Bullard Dillard (Associate Director), Salley (Associate Director), and Davis (Associate Director) communicated via electronic mail to discuss the 2011 SURP application process and deadlines. Each Associate Director is in the process of identifying students to participate in the DOD-funded summer research training program in 2011. The students are submitting their applications to the SURP for consideration.

To broaden the pool of potential applicants, each Associate Director invited faculty and students from his/her institution to participate in the Ernest Just Symposium held on February 25, 2011 at MUSC. A total of 51 students from the three HBCUs attended the symposium (Table 1.). A description of the symposium is included in **Appendix A**. The students who participated in the symposium also received a tour of the MUSC campus and met with MUSC faculty members who could become their future summer research mentors. The DOD grant funds covered travel expenses for two faculty members from Voorhees College who requested travel assistance. All other individuals listed paid for their own travel.

Table 1. Ernest Just Symposium Student Attendees	
Student Names	Institution
Courtney Anderson	Claflin University
Keaira Berry	Claflin University
Camille Brown	Claflin University
Dorneisha Brown	Claflin University
Maurissa Charles	Claflin University
Jasmine Elliot	Claflin University
Kayla Felix	Claflin University
Jessica Fuller	Claflin University
Kendrick Henderson	Claflin University
Khirston Howard	Claflin University

Candice Jenkins	Claflin University
Marleah Johnson	Claflin University
Lakia Mansell	Claflin University
Ezinne Mong	Claflin University
Torez Moody	Claflin University
Britanny Orange	Claflin University
Lynelle Pompey	Claflin University
Donna Sellers	Claflin University
Muhammad Sheraz	Claflin University
Faith Simmons	Claflin University
Minakchhi K. Singh	Claflin University
Ericka Smith	Claflin University
Destynei Tiller	Claflin University
Tamara Wilks	Claflin University
Brook Williams	Claflin University
Rachael Woods	Claflin University
Total Students From Claflin University= 26	
Jasmine Addison	Voorhees College
Brittany Allen	Voorhees College
Tandria Allen	Voorhees College
Kalin Bright	Voorhees College
Latgera Brunson	Voorhees College
Derickeo Cooper	Voorhees College
Ieshia Cooper	Voorhees College
Jessica Dingle	Voorhees College
Katrina Dunn	Voorhees College
Jamie Eaddy	Voorhees College
Hollie Garnett	Voorhees College
Willette Hudson	Voorhees College
John Jackson	Voorhees College
Monica Johnson	Voorhees College
Antavius Jones	Voorhees College
David Maloney	Voorhees College
Edward McMorris	Voorhees College
Tyquan Parker	Voorhees College

Student Names	Institution
Javasha Scott	Voorhees College
Branton Smith	Voorhees College
Britney Smith	Voorhees College
Thomas Sumter	Voorhees College
Dabien Turner	Voorhees College
Brionca Walker	Voorhees College
Kendrea Williams	Voorhees College
Total Students from Voorhees College= 25	

(d) Match the Student Fellows with Their Research Mentors at MUSC (Year 1, months 1-3; Year 2, months 1-3; Year 3, months 1-3)

The Student Fellows were matched with their Research Mentors at MUSC based on the expressed interests of the Student Fellows. For example, Ms. Scharan Clarke expressed an interest in clinical research in her application, so she was matched with Dr. Harry Clarke (no relation) a urologist who conducts prostate cancer clinical research at MUSC. Ms. Clarke had an opportunity to shadow Dr. Clarke as he conducted his clinical research. Table 2. shows the names of the students who participated in the 2009 DOD Collaborative Undergraduate HBCU Student Summer Prostate Cancer Training Program, their Research Mentors at MUSC, and their research topics.

TABLE 2. Summer 2009 DOD Collaborative Undergraduate HBCU Student Summer Prostate Cancer Training Program Students, Mentors, and Research Topics

Student Name	Academic Institution	Research Program	Mentor	Title of Research Project
Mr. DeAngelo Dinkins	SC State University	Department of Defense	Dr. Christina Voelkel-Johnson	Redox protein expression and susceptibility to therapeutic intervention in ARCaP prostate cancer cells
Ms. Ebonie Fuller	SC State University	Department of Defense	Dr. Marvella E. Ford	Evaluating an Intervention to Improve Perceptions of Cancer Clinical Trials among Racially Diverse Communities in South Carolina
Mr. Jonathan Brown	Claflin University	Department of Defense	Dr. Danyelle Townsend	NOV-002 Induces S-Glutathionylation of Serpin A1 and A3 in Human Plasma
Ms. Scharan Clarke	Claflin University	Department of Defense	Dr. Harry Clarke	What Factors Can Predict the Success of Sacro neuromodulation When Used in Patients with Urinary Retention

(e) Hold the Kickoff Intensive and Luncheon (Year 1, months 4-6; Year 2, months 4-6; Year 3, months 4-6)

The Kickoff Intensive and Luncheon took place during the first meeting of the didactic training program in prostate cancer research, on Thursday, June 8, 2010. Dr. Ford gave an overview of the DOD Collaborative Undergraduate HBCU Student Summer Prostate Cancer Training Program. On June 17, 2010, the Associate Directors from the partnering institutions gave presentations to the students. Their presentations highlighted their cancer disparities research.

Task 1 Deliverables: Four Student Fellows were identified, recruited to participate in the program, and admitted to the DOD Collaborative Undergraduate HBCU Student Summer Prostate Cancer Training Program. The Student Fellows were matched with Research Mentors at MUSC, with whom they conducted research in the summer of 2010.

Task 2. Provide Training in Biomedical and Prostate Cancer Research

(a) Conduct Aim 1: Training in the Basics of Research Design and Methods through participation in the MUSC Summer Undergraduate Research Program (Year 1, months 6-8; Year 2, months 6-8; Year 3, months 6-8)

The Student Fellows participated in an intensive training program in the Basics of Research Design and Methods through participation in the MUSC Summer Undergraduate Research Program. The 2010 SURP curriculum is included in **Appendix B**.

(b) Conduct Aim 2: Prostate Cancer Research Training (Year 1, months 6-8; Year 2, months 6-8; Year 3, months 6-8)

The Student Fellows participated in an intensive training 10-week program in Prostate Cancer Research. Four lectures focused on population science, one lecture focused on statistical methods in prostate cancer research, four lectures highlighted prostate cancer clinical research, and four lectures emphasized prostate cancer basic science research. Other lectures described funding opportunities available to the students, career development opportunities, qualitative research methods, perspectives of prostate cancer among community members, and tips for preparing graduate school applications. Disparities research was a cross-cutting theme in all of the lectures. Table 3 below illustrates the curriculum. The presentations given by the lecturers are included in **Appendix C**. Please note that not all lecturers utilized PowerPoint presentations. Some lectures were conducted via roundtable discussion with no slide presentations.

Table 3. Prostate Cancer Research Training Course – Summer of 2010

Week	Topic	Instructor and Organizational Affiliation	Location and Time
Week 1 Tuesday, June 8, 2010	Welcome and Overview	Marvella E. Ford, Ph.D. , Associate Director, Cancer Disparities Program, Associate Professor, Department of Medicine, Division of Biostatistics & Epidemiology Melanie S. Jefferson, MPH , Program Coordinator, Cancer Disparities Program, HCC	Room 124 1:00-2:00pm
Week 1 (Basic Science Research Lecture) Wednesday, June 9, 2010	Overview of the Hollings Cancer Center	Andrew S. Kraft, M.D. , HCC Director, MUSC	Room 121 1:00-2:00pm
Week 2 Thursday, June 17, 2010	Introduction to Health Disparities Research	Rebecca Bullard-Dillard, Ph.D. , CU; Judith Salley, Ph.D. , SCSU; Leroy Davis, Ph.D. , VC	Room 121 1:00-2:00pm
Week 3 (Clinical Research Lecture) Monday, June 21, 2010	Anatomy and the Function of the Prostate	Harry S. Clarke, M.D. , Ph.D., Associate Dean for Graduate Medical Education and Professor, Urology Services, MUSC	Room 121 3:00-4:00pm
Week 3 (Population Science /Epidemiologic Research Lecture) Tuesday, June 22, 2010	Vitamin D and Prostate Cancer	Sebastiano Gattoni-Celli, M.D. , Professor Radiation Oncology	Room 121 1:00-2:00pm
Week 3 (Clinical Research Lecture) Wednesday, June 23, 2010	Two Part Discussion: • Pursuing a Graduate Dual Degree and • Completing a Residency in Radiation Oncology	Gabrielle Cannick, DDS, Ph.D Leander Cannick, M.D. , Department of Radiation Oncology, MUSC	Room 121 1:00-2:00pm
Week 4 (Basic Science) Tuesday, June 29, 2010	Apoptosis of Prostate Cancer Cells	Christina Voelkel-Johnson, Ph.D. , Assistant Professor, Microbiology & Immunology MUSC	Room 121 1:00-2:00pm
Week 4 (Biostatistical Methods Lecture) Thursday, July 1, 2010	Biostatistical Issues in Prostate Cancer Research	Elizabeth Garrett-Mayer, Ph.D. , Director, HCC Biostatistical Core, Department of Medicine, Division of Biostatistics & Epidemiology	Room 121 1:00-2:00pm
Week 5 (Population Science/Epidemiologic Research Lecture) Tuesday, July 6, 2010	Epidemiologic Issues in Prostate Cancer Research	Anthony Alberg, Ph.D. , HCC Associate Director, Prevention and Control Program, Associate Professor, Department of Medicine Division of Biostatistics & Epidemiology, MUSC	Room 121 1:00-2:00pm
Week 5 (Population Science) Thursday, July 8, 2010	Prostate Cancer Research: Perspectives of Community Members	Debbie Bryant, RN Cancer Disparities Outreach Efforts, Outreach Coordinator, HCC Cancer Disparities Program, MUSC	Room 121 1:00-2:00pm
Week 6 (Biostatistical Methods Lecture) Tuesday, July 13, 2010	Statistical Genetics	Emily Kistner-Griffin, Ph.D. , Assistant Professor, Department of Medicine, Division of Biostatistics and Epidemiology	Room 124 1:00-2:00pm
Week 6 (Basic Science Lecture) Thursday, July 15, 2010	Developmental Transcription Factors in Prostate Cancer	Demetri Spyropoulos, Ph.D. , Associate Professor, Pathology & Laboratory Medicine	Room 121 1:00-2:00pm
Week 7 (Population Science Lecture) Tuesday, July 20, 2010	Qualitative Research Methods	Charlene Pope, Ph.D. , Associate Professor, College of Nursing, MUSC	Room 121 1:00-2:00pm
Week 8 (Population Science Research Lecture) Tuesday, July 27, 2010	Lunch and Lecture	Dr. Marvella E. Ford , Cancer Disparities Program	Room 121 1:00-2:00pm
Week 8 (Population Science Lecture) Thursday, July 29, 2010	Project Sugar: Community-based genetic research project among the Sea Islanders (Gullahs) in South Carolina	Ida J. Spruill, Ph.D. , Assistant Professor, College of Nursing, MUSC	Room 121 12:30-1:30pm
Week 9 (Tips for Preparing Graduate School Applications) Tuesday, August 3, 2010	Improving Graduate School Admission Rates	Cynthia F. Wright, Ph.D. , Assistant Dean for Admissions and Associate Professor, College of Graduate Studies, MUSC	Room 121 1:00-2:00pm
Week 9 (Rehearsals) Thursday, August 5, 2010	Research Presentation Rehearsals and Evaluations 11	All Research Students Dr. Marvella Ford , HCC Ms. Melanie Sweat , Program Coordinator	Room 121 1:00-2:00pm
Week 10 (Rehearsals and Evaluations) Tuesday, August 9, 2010	Research Presentation Rehearsals and Evaluations	All Research Students Marvella Ford, Ph.D Melanie S. Jefferson	TBD

(c) **Sponsor the Student Fellows' Participation in a Graduate Record Examination (GRE) course (Year 1, months 6-8; Year 2, months 6-8; Year 3, months 6-8)**

All four Student Fellows took the 8-week Kaplan GRE Test Preparation Course. The 2010 course schedule description is detailed below in Table 4.

Table 4. 2010 KAPLAN COURSE SCHEDULE			
SESSION	DAY	DATE	TIME
Session 1: Diagnostic Exam & Orientation	Tuesday	June 8, 2010	6:00-8:30PM
Session 2: Intro to Math Strategies	Tuesday	June 15, 2010	6:00-8:30PM
Session 3: Strategic Short Verbal	Tuesday	June 22, 2010	6:00-8:30PM
Session 4: Arithmetic & Number Properties	Tuesday	June 29, 2010	6:00-8:30PM
Session 5: Reading I & Issue Essays	Tuesday	July 6, 2010	6:00-8:30PM
Session 6: Algebra & Data Interpretation	Tuesday	July 13, 2010	6:00-8:30PM
Session 7: Vocab & Short Verbal	Tuesday	July 20, 2010	6:00-8:30PM
Session 8: Proportions & Geometry	Tuesday	July 27, 2010	6:00-8:30PM
Session 9: Reading II & Argument Essays	Tuesday	August 3, 2010	6:00-8:30PM

Task 2 Deliverables: In the summer of 2010, we provided state-of-the art comprehensive prostate cancer research education and training opportunities for four students from two of South Carolina's HBCUs. We will develop a cadre of scientists who are well-prepared to play a significant role in discovering and testing new prostate cancer biomarkers. These investigators will conduct research spanning the continuum from basic science to clinical science to population-based research.

Task 3. Prepare Tangible Scientific Products

(a) Prepare and present scientific abstracts based on the Student Fellows' prostate cancer research (Year 1, months 10-12, Year 2, months 1-12, Year 3, months 1-12)

(b) Prepare manuscripts that will be submitted to peer-reviewed journals (Year 1, months 10-12, Year 2, months 1-12, Year 3, months 1-12)

Each Student Fellow prepared a scientific research paper that will form the basis of a peer-reviewed publication. Their papers are included in **Appendix D**. Each Student Fellows' PowerPoint presentations are included in **Appendix E**. The Student Fellows are completing manuscripts with their research mentors. Currently, Ms. Co-Danielle Green, a 2009 Student Fellow, has a recent 2011 peer-reviewed publication stemming from her summer research project,¹ and another manuscript has been submitted for peer-review that includes two additional Student Fellows as co-authors. Ms. Green's publication citation is featured below.

Each Student Fellow gave a scientific presentation based on the results of his or her work. In addition, one Student Fellow, Ebonie Fuller, was selected to give an oral presentation of her summer research project during MUSC's Annual Perry V. Halushka MUSC Student Research Day on November 5, 2010. All four Student Fellows had abstracts accepted for poster presentation at the DOD-sponsored Innovative Minds in Prostate Cancer Today (IMPACT) Conference (plus an additional two Student Fellows from the Summer of 2009). An abstract describing the overall program was also accepted for poster presentation at the conference. **Appendix F** includes the posters that were presented by the Student Fellows and the Program Director and Associate Directors during the IMPACT Conference. **Appendix G** describes the scientific accomplishments of the Student Fellows to date.

Deliverables: Four scientific papers were prepared by the Student Fellows. A cumulative total of nine scientific presentations were given by the four Student Fellows.

REFERENCE

1. Mack JT, Helke KL, Normand G, **Green C**, Townsend DM, Tew KD. ABCA2 transporter deficiency reduces incidence of TRAMP prostate tumor metastasis and cellular chemotactic migration. *Cancer Lett*;300(2):154-61.

Task 4. Evaluate the Training Program

(a) Assess the number of applicants to the Training Program (Year 1, months 1-4, year 2, months 1-4, Year 3, months 1-4)

As planned, four Student Fellows enrolled in the Training Program in the summer of 2010.

(b) Assess the number of Student Fellows who apply to graduate school (Year 2, months 1-12, Year 3, months 1-12)

All four Student Fellows are currently juniors at their perspective institutions, and reported that they have not yet taken the GRE, but plan to take it in their senior year of college.

(c) Assess the number of Student Fellows who are admitted to graduate school (Year 2, months 1-12, Year 3, months 1-12) and (d) Assess the number of graduate schools to which Student Fellows are admitted (Year 2, months 1-12, Year 3, months 1-12)

The Student Fellows have not yet applied to graduate schools. They report that they anticipate applying to graduate programs in their senior year of college.

(e) Identify the number of scientific abstracts presented and peer-reviewed publications that result (Year 1, months 10-12, Year 2, months 1-12, Year 3, months 1-12)

Each Student Fellow gave a scientific presentation during the SURP. In addition, the Student Fellows were invited for poster presentation based on their submitted abstracts to the Innovative Minds in Prostate Cancer Research Today (IMPACT) conference that took place in Orlando, FL on March 9-12, 2011.

Deliverables: The four Student Fellows who participated in the Training Program in the summer of 2010, all of whom are juniors in college, have stated that they have not applied to or been accepted in a graduate program thus far. All of the Student Fellows reported that they will apply to graduate programs in their senior year of college. Each Student Fellow gave a scientific presentation and submitted a scientific paper as part of the SURP. All of the Student Fellows gave poster presentations at the IMPACT conference in March 2011.

We also asked the Student Fellows to evaluate the Training Program. The results are presented in Table 5. It is important to note that all of the Student Fellows rated the program favorably. A summary of the analyses is bulleted below.

- 100% (n=4) Agreed/Strongly Agreed that the summer program was a good research experience

- 100% (n=4) Strongly Agreed that the summer program helped them learn the fundamentals of prostate cancer and research
- 100% (n=4) Agreed/Strongly Agreed that the prostate cancer curriculum was interesting and convenient for learning
- 100% (n=4) Strongly Agreed that they would recommend this program to other students at their college/university

TABLE 5. SUMMARY RESULTS OF STUDENT EVALUATIONS (N=4)

Survey Item	Strongly Disagree		Disagree		Not Sure		Agree		Strongly Agree	
	(N	%)	(N	%)	(N	%)	(N	%)	(N	%)
1. Overall, the summer program was a good research experience.	0	0.0	0	0.0	0	0.0	1	25.0	3	75.0
2. The summer program helped me learn the fundamentals of prostate cancer and research.	0	0.0	0	0.0	0	0.0	0	0.0	4	100.0
3. The KAPLAN Graduate Record Examination (GRE) Course was effective in helping me to learn GRE test preparation strategies.	0	0.0	0	0.0	1	0.25	3	0.75	0	0.0
4. The seminar schedule was convenient.	0	0.0	0	0.0	0	0.0	2	0.50	2	0.50
5. The seminar topics were of interest to me.	0	0.0	0	0.0	0	0.0	3	0.75	1	0.25
6. Participating in the program helped to strengthen my desire for a career in cancer research.	0	0.0	0	0.0	0	0.0	1	0.25	3	0.75
7. The Program Director (Dr. Ford) was accessible and assisted me when needed.	0	0.0	0	0.0	0	0.0	1	0.25	3	0.75
8. The Program Coordinator (Ms. Sweat) was accessible and assisted me when needed.	0	0.0	0	0.0	0	0.0	0	0.0	4	100.0
9. My research mentor was accessible and assisted me when needed.	0	0.0	0	0.0	0	0.0	1	0.25	3	0.75
10. I would recommend this program to other students at my college/university.	0	0.0	0	0.0	0	0.0	0	0.0	4	100.0

REPORTABLE OUTCOMES

Student Summer Research Summaries

Each Student Fellow prepared a research paper and gave a scientific presentation to their peers, mentors and other faculty on August 6, 2010 at MUSC. The manuscripts developed by the Student Fellows are included in **Appendix D** and the scientific presentations are included in **Appendix E**.

Student's Name	Institution	Research Title	Research Summary
Jonathan Brown	Claflin University	NOV-002 Induces S-Glutathionylation of Serpin A1 and A3 in Human Plasma	The objective of the experiment was to identify the S-glutathionylation patterns of serpins in plasma from cancer patients via Western blot analysis. The results concluded that cancer patients have different Serpin A1 and A3 glutathionylation amounts after receiving the NOV-002 treatment. Therefore proving that S-glutathionylation of serpins occur after receiving the chemotherapeutic or drug, NOV-002.
Scharan Clarke	Claflin University	What Factors Can Predict the Success of Sacro neuromodulation When Used in Patients with Urinary Retention	The objective of this study was to determine if any preoperative factors could help predict better clinical outcomes in the setting of urinary retention. Performed a retrospective chart review from 2000 to 2010 of procedures performed by three dedicated voiding dysfunction specialist. The preoperative and intraoperative factors evaluated do not appear to give us significant prognostic data
DeAngelo Dinkins	SC State University	Redox Protein Expression and Susceptibility to Therapeutic Intervention in Arcap Prostate Cancer Cells	Thioredoxin is a redox-regulating protein that plays a central role in regulating cellular redox and preventing cell death. It was hypothesized that increased expression of redox proteins is an underlying cause for the aggressive, therapy-resistant prostate cancer phenotype.
Ebonie Fuller	SC State University	Evaluating an Intervention to Improve Perceptions of Cancer Clinical Trials among Racially Diverse Communities in South Carolina	The objective of the study was to conduct a cancer clinical trials education intervention with racially diverse groups in South Carolina. The intervention consisted of a 30-minute cancer clinical trial educational presentation. Providing cancer clinical trials information to racial and ethnic minorities led to more positive perceptions of cancer clinical trials. It was concluded that ARCaPm cells do have an increased expression of redox proteins. Therefore they are more resistant to cancer treatments.

Student Summer Research Manuscript Abstracts

Importantly, as noted, all 4 Student Fellows from 2010 plus an additional 2 Student Fellows from the Summer of 2009 submitted abstracts for presentation consideration during DOD-sponsored Innovative Minds in Prostate Cancer Today (IMPACT) Conference in March 2011. All of the abstracts were accepted for poster presentation. An abstract describing the overall research training program was also accepted for poster presentation at the IMPACT Conference. Each abstract is listed below. Communications between all institutional directors, faculty advisors, and research mentors took place to assist the students with the development of their poster presentations. All institutional directors (Drs. Ford, Bullard-Dillard Salley, and Davis) participated in the IMPACT Conference.

Jonathan Brown
Claflin University

ABSTRACT

NOV-002 Induces S-Glutathionylation of Serpin A1 and A3 in Human Plasma

Introduction: Serine protease inhibitors (serpins) make up about 2% of the total protein in human serum. Serpins have been found to undergo post-translational modification, S-glutathionylation, in patients treated with redox chemotherapeutics. S-glutathionylation is the specific posttranslational modification of protein cysteine residues by the addition of glutathione. S-glutathionylation alters the functionality of enzymes, receptors, structural proteins, transcription factors, and transport proteins.

Methods: The methods evaluated the effects of the redox chemotherapeutics on the S-glutathionylation of serpins. NOV-002, is the redox chemotherapeutics utilized to cause serpin A1 and A3 to glutathionylate in treated serum. After receiving the redox chemotherapeutics, glutathionylated Serpin A1 and A3 were used to analyze myeloproliferative events. Protein electrophoresis and Western blot analysis were utilized to test glutathionylation. Glutathionylation of serpin A1 and A3 proteins was measured before and after the addition of the drug NOV-002 to serum samples of cancer patients.

Results: According to the Western blot analyses, the glutathionylation patterns in both blots illustrated that glutathionylation was increased in the plasma samples that were treated with NOV-002. On the contrary, the plasma samples that were not treated with NOV-002 had less glutathionylation patterns compared to those that were treated with the drug. This western blot that was done on the serpin group, Serpin A1 illustrated that Serpin A1 were found in all of the eight plasma samples taken from cancer patients and were S-glutathionylated.

Conclusion: The results revealed that cancer patients have different Serpin A1 and A3 glutathionylation amounts after receiving the NOV-002 treatment. This supports our hypothesis that S-glutathionylation of serpins occur after receiving the chemotherapeutic or drug, NOV-002.

Impact: The results of this study could lead to improved hematopoietic cell mobilization in bone marrow cells, which could lead to significant increases in white blood cell counts in cancer patients. Currently, many cancer patients experience low white blood cell counts following receipt of chemotherapy.

ABSTRACT

What Factors Can Predict the Success of Sacroneuromodulation When Used in Patients with Urinary Retention?

Introduction: Urinary retention issues are a side effect of some types of prostate cancer treatment. Sacroneuromodulation has been used for both detrusor over-activity and urinary retention. The exact mechanism of action is not known for this therapy. We sought to determine pre-operative factors that could predict good clinical outcomes in the setting of urinary retention.

Methods: We performed a retrospective chart review of procedures performed by three dedicated voiding dysfunction specialists from years 2000-2010. Characteristics evaluated included patient's age, previous surgeries, neurologic diagnosis, length of retention, invasive and noninvasive urodynamic data. Operative data collected included presence of bellows response, sacral foramen used, number of leads, number of electrodes generating a response, side of lead, and complications. Postoperative data included subjective and objective improvement, progression to IPG implantation, wound infection, complications and need for revision.

Results: We identified 54 patients who underwent 73 sacroneuromodulation lead placements as treatment for urinary retention. Seventeen of the 54 patients were males and 35 were females. Their mean age was 50 years. Twenty-seven patients had data on length of retention with a mean of 34 months. Twenty-four patients had undergone previous surgery and 18 were on medical management. All patients underwent urodynamic testing and demonstrated little or no detrusor contraction low flows and elevated post void residuals (PVR). Mean detrusor pressure was 12.5cm /H₂O, mean flow rate was 4cc/sec and mean PVR was 593cc. Only 3 patients presented with a neurologic diagnosis. All 73 lead placements demonstrated a good bellows response. Thirty-six leads were placed in the left and 36 on the right; one was not recorded. Bilateral stimulation was tested in 67 patients. A mean of 2.4 electrodes generated a response after lead implantation. Subjective improvement was noted after 48 lead placements and 47 went on to implantable pulse generators (IPG). Twenty six lead placement procedures did not go on to IPG. When comparing the procedures that failed to go on to IPG verses those that did we found few differences. The mean age was higher in the failure group 55 vs. 43years. Mean PVR was also found be higher in the failure group 613cc verses 570cc. No difference was noted in mean flow rate, max detrusor pressure, or number of stimulating electrodes.

Conclusions: The pre-operative and intra-operative factors we evaluated do not appear to give us significant prognostic data. The mechanism of action of sacroneuromodulation lead placements and the factors that may portend its success have yet to be fully defined.

Impact: This study described a potential solution to treating urinary voiding dysfunction, which is a side effect of prostate cancer treatment that has a significant negative impact on quality of life. Electrical impulses through neuromodulation have been theorized to help patients with urinary retention and urinary incontinence by restoring control of the detrusor and sphincter muscles. The findings from this study show that further clinical investigation into the mechanism of sacroneuromodulation lead placements is warranted.

ABSTRACT

Redox Protein Expression and Susceptibility to Therapeutic Intervention in ARCaP Prostate Cancer Cells

Background: Prostate cancer is the 2nd leading cancer in men after lung cancer. Thioredoxin is a redox-regulating protein that plays a central role in regulating cellular redox and preventing cell death in prostate cancer. There is a high expression of thioredoxin in prostate cancer cells because the tumor environment is usually under either oxidative or hypoxic stress and both stresses are known to be up-regulators of thioredoxin expression. Indolent disease can be treated fairly well and progresses slowly. However, the more aggressive form of prostate cancer spreads throughout the body and there are no curative treatments.

Hypothesis: We tested the hypothesis that increased expression of redox proteins is an underlying cause for the aggressive, therapy-resistant prostate cancer phenotype.

Methods: In our project we looked at the expression of redox proteins and susceptibility to chemotherapy in ARCaPe and ARCaPm cells. Using western blot methods and Image J we were able to quantify the expression of thioredoxins. Susceptibility to chemotherapy was tested in a viability assay.

Results: Western blot analysis indicated increased expression of the redox proteins such thioredoxin 1 and thioredoxin 2 in ARCaPm cells when compared to ARCaPe cells. Our results conclusively showed that Taxol killed both cell types, while Depsipeptide proved effective on ARCaPe cells and ineffective on the ARCaPm cells. We are currently determining the effect of combination therapies.

Conclusions: In conclusion we found that ARCaPm cells do have an increased expression of redox proteins. Therefore they are more resistant to cancer treatments, such as depsipeptide.

Impact: The results lend evidence for possible combination therapies to effectively treat aggressive prostate cancer phenotypes. Thus, the study results could potentially lead to improved clinical treatment for aggressive prostate cancer, which currently has extremely poor prognostic outcomes.

ABSTRACT

Evaluating an Intervention to Improve Perceptions of Cancer Clinical Trials among Racially Diverse Communities in South Carolina

Objective: To conduct a cancer clinical trials education intervention with racially diverse groups in South Carolina.

Methods: The study was conducted at ten different sites in eight counties in South Carolina. The intervention consisted of a 30-minute cancer clinical trial educational presentation. Participants were recruited primarily by community partners. Pre- and post-intervention surveys were administered. The survey instrument included seven items. Sample items included the following: “Do you think that patients should be asked to take part in medical research?” and “Would you be prepared to take part in a study where treatment was chosen at random?” Analyses were completed using SPSS 16.0, SAS 9.1.3, and R v2.6.1.

Results: The study sample consisted of 195 predominantly African American participants (n=195). One hundred and ninety participants reported their age and most were 50+ years (57.4%). Among those who reported income (n=182), 66.6% had an annual household income < \$60,000. For each of the seven survey items assessing perceptions of cancer clinical trials, respectively, 9%, 24%, 38%, 20%, 18%, 14% and 13% of the participants changed to more favorable responses on the post-test vs. pre-test ($p < 0.001$).

Conclusions: Providing cancer clinical trials information to racial and ethnic minorities led to more positive perceptions of cancer clinical trials. Future research studies could incorporate a longer follow-up period to assess the behavioral impact of the intervention and whether short-term gains are sustained over time.

Impact: Despite their higher incidence and mortality of cancer relative to their European American counterparts, African Americans are not well represented in cancer clinical trials. The intervention that we tested led to more favorable perceptions of clinical trials in a predominantly underrepresented population. Future studies could evaluate whether the significant and positive changes in perceptions of clinical trials translate into higher rates of clinical trials enrollment.

ABSTRACT

Enhancing Gene Delivery to Cancer Cells

Background: Adenoviral delivery to cancerous cells has potential as a new therapy but is also problematic. Many cancer cells lack coxsackie and adenovirus receptor (CAR) which serves as the transduction factor for an adenovirus to enter a cell. HDACi and polymers have been proven to enhance the transduction of an adenovirus.

Objective: This study involved the investigation of a cell line of prostate cancer cells that infects poorly and to test if HDACi or the polymer EGDE-3,3' will increase the infectivity of the cell line.

Methods: Infectivity and transgene expression was measured by using flow cytometry following exposure to an adenovirus that expresses green fluorescent proteins. From this, the percentage of cells that were GFP positive were calculated. GFP intensity was determined from this as well.

Results: The results indicated that HDACi increased infectivity in the prostate cancer cells more than 5-fold at MOI's below 10. However EDGE-3, 3' did not increase infectivity.

Conclusions: EDGE-3, 3' did not work as well as it did in a previous study using bladder cancer cells. However, there was an increase when HDACi were used along with AdGFP. There was also a notable increase of infectivity in the cells that were treated with AdGFP and depsi-peptide. Therefore, HDACi may have been more suitable for enhancing adenoviral transgene expression in prostate cancer cells.

Impact: Adenoviruses have the potential to be genetically modified and used in gene therapy to treat diseases such as prostate cancer. Favorable outcomes were seen when HDACi were in conjunction with AdGFP. Further studies are needed to test the effectiveness of this treatment.

ABSTRACT

Role of ABCA2 in Prostate Tumor Progression

Background: Prostate cancer is responsible for an estimated 33% of all newly diagnosed cancers in men. Unfortunately, prostate cancer tumors do not always respond to chemotherapy treatment. Therefore, determining what causes the tumors to become resistant is important to efficiently treat the cancer.

Objective: This study involved determining the role of ABCA2 expression and its association with resistance to chemotherapy and multi-drugs. Therefore the study aimed to determine whether ABCA2 is correlated with tumor progression and to determine whether ABCA2 has an effect on the grade of prostate tumors and instances of metastasis.

Methods: To examine the objectives, a knockout line was created using the Transgenic Adenocarcinoma of Mouse Prostate (TRAMP) model and compared to wild types by various methods including: Western Blotting Analysis, PCR, MRI imaging, Vimentin and Desmin analyses, Scratch Assays, and Transient Transfections.

Results: The ABCA2 expression of Vimentin was found to be elevated in TRAMP prostatic epithelia when viewing the sample slides. In the dorsal prostate, ABCA2 expression in dorsal prostate was also elevated in TRAMP compared to WT mice; expression increases over time/progression. Increased oxidative stress markers were in KO TRAMP tissue. Proliferation of prostatic & SV lesions was similar in WT and KO TRAMP tissues. There was a slight elevation of ROS/RNS-induced DNA damage in KO TRAMP prostate epithelia and elevated ROS/RNS-induced 4-hydroxynonenal modified proteins. Seminal vesicle volume was greater in KO TRAMP mice at 20 weeks. Furthermore, normal stroma of KO TRAMP mice had elevated vimentin expression. No change occurred in the expression of desmin, a myocytic marker of stromal cells.

Conclusions: Although prostate tumor progression was similar in both lines, the instances of metastasis were elevated in the knock out mice.

Impact: The study results related to the role of ABCA2 in prostate cancer tumor progression could potentially lead to clinical improvements in treatment to overcome multi-drug resistance and tumor relapse. Future studies could expand this investigation.

Marvella E. Ford, Ph.D. (Medical University of South Carolina)
Rebecca Bullard-Dillard, Ph.D. (Claflin University)
Judith D. Salley, Ph.D. (SC State University)
Leroy Davis, Ph.D. (Voorhees College)

ABSTRACT

Collaborative Undergraduate HBCU Student Summer Prostate Cancer Training Program

Background: There is a critical need to increase the number of racially and ethnically diverse prostate cancer researchers. The purpose of this 3-year project is to develop a prostate cancer research training program at the Medical University of South Carolina (MUSC) with 12 students from the following three Historically Black Colleges and Universities (HBCUs) in South Carolina: Claflin University, South Carolina State University (SCSU), and Voorhees College. Students from the three HBCUs (defined as “Student Fellows”) will participate in research internships in the laboratories/research units of senior prostate cancer research scientists at MUSC.

Specific Aims: Aim 1.) To provide training in the basics of research design and methods to four Student Fellows each year through participation in the MUSC Summer Undergraduate Research Program (SURP); Aim 2.) To immerse four Student Fellows each year in a prostate cancer research training curriculum.

Results: In 2009-2010, eight Student Fellows were identified, recruited to participate and admitted to the DOD Collaborative Undergraduate HBCU Student Summer Prostate Cancer Training Program. The Student Fellows were matched with Research Mentors at MUSC, with whom they conducted research in the summers of 2009 and 2010. Each Student Fellow prepared a scientific paper and gave a scientific presentation at the end of the Training Program. Each Student Fellow also completed an 8-week Graduate Record Examination Test Preparation Course at a local Kaplan Center. In addition, a total of 73 students from the three HBCUs attended the Ernest E. Just Symposium at MUSC in February of 2010. The symposium is used as a platform to recruit racially and ethnically diverse students to MUSC.

Conclusions: In the summers of 2009-2010, we provided state-of-the art comprehensive prostate cancer research education and training opportunities for **eight** Student Fellows from HBCUs in South Carolina. Each Student Fellow prepared a scientific paper and gave a scientific presentation.

Impact Statement: Through this funding mechanism, we are developing a cadre of scientists who are well-prepared to conduct research spanning the continuum from basic science to clinical science to population-based research.

CONCLUSIONS

During the second year of the DOD Collaborative Undergraduate HBCU Summer Prostate Cancer Training Program, the tasks outlined in the Statement of Work were met successfully. Two Student Fellows were recruited from Claflin University and two Student Fellows were recruited from SC State University. Each Student Fellow conducted research and prepared a research paper that was presented at the conclusion of the program. The Student Fellows also presented their work at the national Department of Defense-sponsored IMPaCT meeting. The recruitment process for the 2011 Student Fellows is ongoing.

Two additional students from Voorhees College participated in the DOD Collaborative Undergraduate HBCU Summer Prostate Cancer Training Program using funds leveraged from another DOD grant that was funded in 2010 (DOD Grant Number W81XWH-10-2-0057, Southeastern Virtual Institute for Health Equity and Wellness). The DOD SE VIEW grant will provide funding for only two additional students per year. The following table lists each student's name, college, and research summary.

Student's Name	MUSC Research Mentor	Research Title	Research Summary
Edward McMorris	Dr. James Norris	Acid Ceramidase Overexpression Causes Activation of and Addiction to AKT Signaling in Prostate Cancer	Previous studies have demonstrated the role of the ceramide metabolizing enzyme acid ceramidase in promoting an aggressive cancer phenotype in prostate cancer cell lines. In addition, it has been found that greater than 80% of prostate tumors overexpress acid ceramidase, suggesting that acid ceramidase may be an important mediator of development and progression of prostate cancer. In this study, we demonstrate that the increased rate of proliferation in acid ceramidase overexpressing cells is dependent on signaling through the oncogenic PI3K/Akt pathway. In addition, we found that acid ceramidase overexpressing cells are more sensitive to Akt inhibition than control cells, suggesting that acid ceramidase overexpressing tumors are addicted to Akt signaling. These findings highlight the importance of investigating the Akt pathway as a potential therapeutic target in acid ceramidase overexpressing tumors.

Student's Name	MUSC Research Mentor	Research Title	Research Summary
Janielle Samuel	Dr. Danyelle Townsend	Protein Glutathionylation Levels In MCF7 Breast Cancer Cells Expressing Glutathione S-transferase Pi Isoforms	S-Glutathionylation is a redox- regulated posttranslational modification of protein cysteine residues by the addition of the tripeptide glutathione. It is promoted by oxidative and nitrosative stress. The disulfide bond between glutathione and a protein is reversible. S- Glutathionylation is similar to phosphorylation because it alters protein structure and function such as activation of protein enzyme activity. S-glutathionylation alters the function of enzymes, receptors and structural proteins. S-glutathionylation if proteins are critical to cellular stress response but the characteristics of the forward reaction are not completely known. However, results have shown that GSTpi potentiates S-glutathionylation reactions. Glutathione S- transferase pi is a subgroup of GST family. The GSTpi gene is polymorphic gene encoding active, functionally different GSTpi proteins which provides cellular protection against free radical and carcinogenic compounds. The first reported example of kinase regulation by a GST was in the inhibition of c-Jun aminoterminal kinase (JNK) by a pi class. JNK a stress activated kinase, has been implicated in pro-apoptotic signaling and my mediate the cytotoxicity of a variety of chemotherapeutic agents. We discovered that MCF7 breast cancer cells expressing GST pi isoforms exhibit different glutathionylation levels in response to nitrosative stress. Future research is needed to further elucidate these relationships.

APPENDICES

APPENDIX A
Ernest Just Scientific Symposium February 25, 2011

8:00-9:00 am Registration and Breakfast-BSB 100 entrance to Auditorium

9:00-9:10 am *Opening:* Mark S. Sothmann, Ph.D., Interim Vice President for Academic Affairs and Provost MUSC
 Steven Lanier, Ph.D., Associate Provost for Research; Professor of Pharmacology, MUSC
Greetings: Dr. Sabra Slaughter; Chief of Staff, Office of the President MUSC



9:10-9:40 am **History** Title: *"Ernest Everett Just/ History and Retrospective, Philosophical Analysis of the birth of Omega Psi Phi Fraternity, Inc."*
 Charles A. Christopher, MD
 Surgeon General for Omega Psi Phi Fraternity, Inc.
 Retired Contract physician
 Austin, Texas



9:40-10:10 am Title: None Shall Perish
 Kelly M. Mack, Ph.D.
 Program Director, ADVANCE
 National Science Foundation
 Arlington, Virginia

10:10-10:30 am Break



10:30-11:15 am Just Symposium Title: Human Defibrillation: History & Evolution
 Key Note Dr. Levi Watkins, MD
 Professor of Cardiac Surgery,
 Associate Dean, School of Medicine
 The Johns Hopkins Hospital
 Baltimore MD

11:20-11:35 am Title: TBA
Student Presenters

BREAKOUT SESSIONS (middle and high school students from Baltimore, MD-room 402)

11:35 - 12:20 pm Dr. Clifton Poodry, Ph.D; Director, Division of Minorities in Research; National Institute of General Medical Sciences; National Institutes of Health
Campus tour for visiting students, Undergraduate Advisors meet with MUSC College Admissions Officers

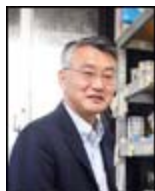
12:25-12:55 pm LUNCH



1:05-2:00 pm Title: Epithelial plasticity and the origin of fibroblasts
Eric Neilson, MD
Thomas Fearn Frist, Sr Professor in Medicine
Professor of Cell and Developmental Biology
Vanderbilt University School of Medicine
Nashville, TN



2:05-3:00 pm Title: Respecification of cell type using transcription factors
Jonathan Slack, Ph.D.
Professor and Director Stem Cell Institute
University of Minnesota
St. Paul Minnesota



3:05-4:00 pm Title: Periostin in fibrillogenesis for tissue regeneration
Akira Kudo, Ph.D.
Professor
Department of Biological Information
Tokyo Institute of Technology
Yokohama Japan

APPENDIX B
MUSC SURP SCHEDULE FOR 2010

Summer Undergraduate Research Program Lecture Series

Summer 2010

Location: BSB 302, 8:30-9:30 AM

<i>Date</i>	<i>Topic</i>	<i>Lecturer</i>
June 8	What is Translational Research?	Dr. Kathleen T. Brady M.D., Ph.D.
June 9	The Development of a New Treatment and Diagnostic Test for Bladder Cancer: From Bench to Bedside	Dr. Perry Halushka, PhD, MD
June 10	Human Subject Research Success Center: How Scientists Get Help Conducting Research	Dr. Susan C. Sonne, PharmD./ Royce Sampson, MSN, RN
June 11	Treatment of Cocaine Addiction: From Bench to Bedside	Khaled Moussawi, MD/PhD Student
June 14	Hepatic Steatosis in a Growing World: The Impact of Transplantation	Dr. Kenneth Chavin, MD, PhD
<u>Responsible Conduct of Research – MANDATORY – 8:30 – 10:20 am</u>		
June 15	MANDATORY: Public Perceptions of Scientific Research –Questionable Research Practices (“And the Band Played On” video and discussion)	Dr. Ed Krug, PhD Dr. Titus Reaves, PhD
June 16	MANDATORY: Moral Reasoning in Ethical Dilemmas (lecture and case study discussion)	Dr. Ed Krug, PhD
	Mentoring (lecture and discussion)	Dr. Ed Krug, PhD
	Responsible Lab Citizenship	Dr. Ed Krug, PhD
June 16	(C) Cancer Cell Cycle (lunch meeting location TBA)	Dr. Cynthia Wright, PhD
June 17	MANDATORY: Data Management/Data Manipulation (Lecture and case study discussion)	Dr. Ed Krug, PhD
	Authorship and Plagiarism (lecture and case study discussion)	Dr. Ed Krug, PhD
June 18	MANDATORY: Animal Use in Research (lecture & discussion)	Dr. Alison Smith, PhD
	Research Misconduct/Whistleblower Protections (lecture and literature discussion)	Dr. Ed Krug, PhD
	Closing Comments/Exit Evaluation	
<u>Outside Assignment:</u> Complete the University of Montana On-Line RCR training (link below) by June 14th - you must score a minimum of 70% on all quizzes. Bring paper copies of quiz completion with you to the RCR Lectures starting on June 15th. (http://ori.dhhs.gov/education/products/montana_round1/research_ethics.html)		
June 21	Lipidomics	Dr. Maurizio Del Poeta, MD
June 22	Stem Cells	Dr. Amanda LaRue, PhD
June 23	Cell Biology – Tissue Ultrastructure	Dr. Debra Hazen-Martin, PhD
June 23	(M) Introduction to Oceans and Human Health (8:30-9:30)	Jillian Lynch
	Climate Change Game – Mitigation Strategies (9:30-10:30)	Dr. Kristin Hardy, PhD Dr. Mackenzie Zippay, PhD

June 24	Developmental Biology	Dr.	Michael Kern, PhD
June 24	(M) Harmful Algal Blooms (HABs) and Their Impact on Human Health (8:30-9:30am)	Dr. Fran Van Dolah, PhD	
	Discussion (9:30-10:30am)	Peter Feltman	
June 25	Proteomics Technology	Dr.	Lauren Ball, PhD
June 28	(H) The Heart		Dr. Perry Halushka, PhD, MD
June 29	Confocal/Multiphoton Microscopy of Living Cells		Dr. John Lemasters, MD, PhD
	And Tissues		
June 30	Microarray Analysis	Dr.	Jeremy Barth, PhD
June 30	(M) Algal Biofuels (9:30-10:30am)		Dr. Chris Hintz, PhD
	Discussion (10:30-11:30am)	Amber Wilkinson	
July 1	Recombinant DNA	Dr.	David Kurtz, PhD
July 2	Transcription	Dr.	Steven Kubalak, PhD
July 5	(M) Epidemiology and Human Health (8:30-9:30am)		Dr. Tom Hulsey, PhD
July 6	(H) Electrical Properties of the Heart	Dr.	Rupak Mukherjee, PhD
July 6	(M) Pre-term Birth and the Environmental Connection Part I (12:00-1:30pm)	Dr.	Dr. Roger Newman, PhD
July 7	(C) Cytogenetics		Ramsey Unal, PhD
July 7	(M) Links Between Alzheimers Disease and the Marine Environment (8:30-9:30am)		Dr. Daynna Wolff, PhD
July 8	(N) Retinoids & Vision		Dr. Mark Kindy, PhD
July 8	(M) Marine Mammal Surfactants and Their Role in Role in Pre-Term Birth Defects (8:30-9:30am)		Dr. Masahiro Kono, PhD
	Visit Premature Infant Clinic (9:30-11:30am)		Dr. John Baatz, PhD
July 9	G Proteins		
July 9	(M) Causes and Consequences of Disease in Marine Sentinell Species (MSS) (8:30-9:30am)	Dr. John Hildebrandt, PhD	Dr. Lori Schwacke, PhD
	Discussion (9:30-10:30am)	Leslie Burdett	
July 12	(H) Arterial Pressure Control & High Blood Pressure		Dr. Perry Halulshka, PhD, MD
July 12	(M) Oceans and Human Health Part II (8:30-9:30am)		Jillian Lynch
	Discussion (9:30-10:30am)	Dr.	Kristin Hardy
	How to make a poster (12:00-1:00pm)	Dr.	Mackenzie Zippay, PhD
July 13	(N) Dementia	Dr.	Mark Kindy, PhD
July 13	(M) Ecotoxicology: A Survey of Marine Contaminants and the Consequences (8:30-9:30am)	Krystal Ludwig	Dr. Geoff Scott, PhD
	Discussion: Contaminants of Emerging Concern (9:30-10:30am)		
July 14	(N) ADD/ADHD	Dr.	Tomas Tampa, PhD
July 14	(M) Marine Natural Pharmaceutical Products (8:30-9:30am)		Dr. Peter Moeller, PhD
	Discussion (9:30-10:30am)		Matt Bertin
July 15	(C) Kinds of Cancer		Dr. Robert Gemmill, PhD
July 15	(M) Natural Products in the Clinic (8:30-9:30am)		Dr. Mike Wargovich
	Discussion (9:30-10:30am)	Dina Brown	
July 16			
July 16	(M) The Global Context of OHH (8:30-9:30am)		Dr. Juli Trtanj
	NOAA Structure & Opportunities (9:30-10:30am)		
	MBES Student Research Day (12:00-4:00pm)		

July 19	(N) Addiction & Alcohol	Dr.	Scott Stewart, MD
July 20	Receptors	Dr.	Steven Rosenzweig, PhD
July 20	(M) Powerpoint Presentation Workshop		
July 20	(M) Alternative Careers in Science (12-1pm)		Dr. Craig Plante, PhD
July 21	(C) Herbals & Cancer	Dr.	Michael Wargovich, PhD, FACN
July 22	(N) Neuroimaging lab demonstration		Dr. Mark George, MD
July 23	(C) Epidemiology of Cancer		Dr. Kristin Wallace, PhD
July 26	(M) Ecology of Human Pathogens in Coastal and Other Natural Waters (8:30-9:30am)		Dr. Erin Lipp, PhD
	Discussion: Pathogens in the Marine Environment – A Public Health Perspective (9:30-10:30am)		
July 26	(H) Atherosclerosis	Dr.	Samar Hammad, PhD
July 27	(C) Cancer Chemotherapy	Dr.	David Kurtz, PhD
July 27	(M) Marine Science Media and Communication (12-1pm)		Dr. Carolyn Sotka, PhD
July 28	(N) Neuroimaging	Dr.	Mark George, MD
July 29	(H) Kidney	Dr.	Ed Soltis, PhD
July 30	(H) Imaging the Heart		Dr. Joseph Schoepf, MD
Aug 2	(N) Spinal Cord Injury		Dr. Narendra Banik, PhD
Aug 3	(N) Schizophrenia	Dr.	Antonieta Lavin, PhD
Aug 4	(C) Pathology Museum		TBA
Aug 5	H) Aspirin & NSAIDS	Dr.	Perry Halushka, PhD,
MD			
Aug 6	(N) Addiction & Drugs		Dr. Kimber Price, PhD
Aug 9	Presentations (all day)		
Aug 10	Presentations (all day)		
Aug 11	Presentations (all day)		
Aug 12	Presentations (if another day is needed)/students will finish up with mentors and the dean's office		
Aug 13	Final checks disbursed, all paperwork turned in, labs cleared out		

Note: Lectures in Black are for all students.

Lectures in Blue are for Cardiovascular track students. (7 lectures)

Lectures in Red are for Cancer track students. (7 lectures)

Lectures in Green are for Neuroscience track students. (9 lectures)

Lectures in Orange are for Marine Biomedicine (Ocean & Human Health) track students. Location:

The White House at Fort Johnson

CTSA – (5 lectures)

APPENDIX C
Chronological Listing of PowerPoint Presentations by Lecturers

NOTE: Not all lecturers utilized a PowerPoint presentation. Instead, some lectures were conducted through roundtable discussion. Therefore, all lectures may not be presented in this appendix.

WELCOME!

DOD and RBC HBCU Collaborative Undergraduate Research Students

Principal Investigator:

MUSC: Marvella E. Ford, PhD

Co-Investigators:

SC State University: Judith D. Salley, PhD

Clafin University: Rebecca Bullard-Dillard, PhD

Voorhees College: Leroy Davis, PhD

Program Coordinator:

Melanie Sweat Jefferson, MPH



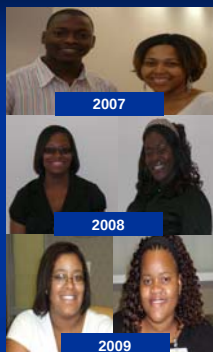
Hollings Cancer Center (HCC) Cancer Disparities Program, 5-Point Action Plan Objectives

1. Conduct cancer disparities activities with partners in South Carolina (SC)
2. Develop specific, targeted research interventions to reduce cancer disparities
3. **Increase the number of investigators in SC who conduct cancer disparities research**
4. Increase use of products and/or services provided by minority-owned businesses in SC
5. Provide training in cultural competence

Increasing the Number of Investigators in SC who Conduct Cancer Disparities Research

RBC Research Scholars Program

- Five year grant established by the Royal Bank of Canada (RBC) Insurance Company in 2007
- In partnership with Voorhees College
- Two RBC Research Scholars per year participate in MUSC's 8-week Summer Undergraduate Research Program (SURP)



Increasing the Number of Investigators in SC who Conduct Cancer Disparities Research (continued)

Department of Defense HBCU Collaborative Undergraduate Student Summer Training Program

- Three-year grant focusing on prostate cancer disparities research
- In partnership with Historically Black Colleges/Universities (HBCUs)
 - Clafin University
 - SC State University
 - Voorhees College
- Scholarships are awarded to four students per year
- Students participate in the SURP and in a prostate cancer research curriculum



Research Outcomes

Each DOD Student Fellow developed a research paper and gave a scientific presentation for their summer research experience on August 6, 2010 at MUSC

Scharan Clarke, Clafin University

■ **Title:** Does the Preoperative Evaluation of Men with Bladder Obstruction Affect the Outcomes of Outlet Reduction Procedures?

■ **Summary:** Evaluate whether preoperative workup affects surgical outcomes in patients with symptomatic urinary obstruction. We retrospectively reviewed our series of 119 patients extracted randomly from 2004 to 2009. In our series more invasive preoperative evaluation did not lead to better clinical outcomes

Research Outcomes

CoDanielle Green, SC State University

■ **Title:** Role of ABCA2 in Prostate Tumor Progression

■ **Summary:** To determine if ABCA2 has a role in prostate tumor progression and metastatic phenotype in mouse (TRAMP/ABCA2 knockout) and cell (D6P2T and PC3 knockdown) models. This was achieved by performing specific assays and analyses relating to the ABCA2 knockout models

Research Outcomes

Andrea Gibson, Claflin University

- **Title:** Enhancing Gene Delivery To Cancer Cells
- **Summary:** Testing HDACi and polymers to see if they will increase infectivity in prostate cancer cells with an adenovirus. The HDACi used are MS275 and depsispeptide and the polymer used is EDGE-3,3'. AdGFP is the adenovirus used in the treatment of cells

Research Outcomes

Samantha Jones, SC State University

- **Title:** Isolation and *ex vivo* expansion of antigen-specific CD8+ T cells
- **Summary:** T cell immunotherapy is a new approach for using the cells of the immune system to treat prostate cancer. The hypothesis was that CD8+ T cells that are specific for prostate antigens could easily be isolated and expanded from the blood of a female donor. We were successfully able to isolate CD8+ T cells and expand them after making them specific for prostate cancer

Research Outcomes

Celina Ridgeway, Voorhees College

- **Title:** Evaluating A Cancer Education Program with Minority Populations in South Carolina
- **Summary:** Lack of knowledge about cancer screening, prevention, early detection, and treatment likely contributes to the cancer disparities. A Train the Trainer educational intervention was used to enhance cancer knowledge in minority populations in South Carolina

Research Outcomes

Rashell Blake, Voorhees College

- **Title:** Improving Perceptions of Cancer Clinical Trials among Minority Populations in South Carolina
- **Summary:** Despite the higher incidence and mortality of cancer in African American population compared to the Caucasian population, African Americans are less likely than Caucasians to participate in cancer clinical trials. A Train the Trainer educational intervention was used to educate minority communities about cancer clinical trials, and increase positive perceptions of cancer clinical trials

Students Are Co-Authors on Peer-Reviewed Publications

- Norell H, Martins da Palma T, Leshar A, Kaur N, Mehrotra M, Naga OS, Spivey N, **Olafimihan S**, Chakraborty NG, Voelkel-Johnson C, Nishimura MI, Mukherji B, Mehrotra S. Inhibition of superoxide generation upon T-cell receptor engagement rescues Mart-1(27-35)-reactive T cells from activation-induced cell death. *Cancer Res.* 2009 Aug 1;69(15):6282-9. Epub 2009 Jul 28.
- Norell H, Zhang Y, McCracken J, da Palma TM, Leshar A, Liu Y, Roszkowski JJ, **Temple A**, Callendar GG, Clay T, Orentas R, Guevara-Patino J, Nishimura MI. CD34-based enrichment of genetically engineered human T cells for clinical use results in dramatically enhanced tumor targeting. *Cancer Immunol Immunother*, online publication, December 2009.
- Ford ME, Wahlquist AE, **Ridgeway C**, **Streets J**, Mitchum KA, Harper R, Hamilton I, Etheredge J, Jefferson MS, Varner H, Garrett-Mayer E. Evaluating an Intervention to Increase Cancer Knowledge in Racially Diverse Communities in South Carolina. (In Press in *Patient Education and Counseling*.)

Summer Activities

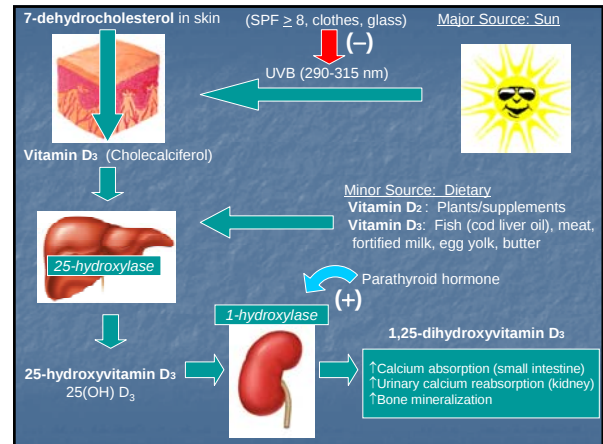
- Prostate Cancer Research Training Curriculum
- KAPLAN GRE Prep Course
- SURP Activities
- Final Research Project

QUESTIONS?

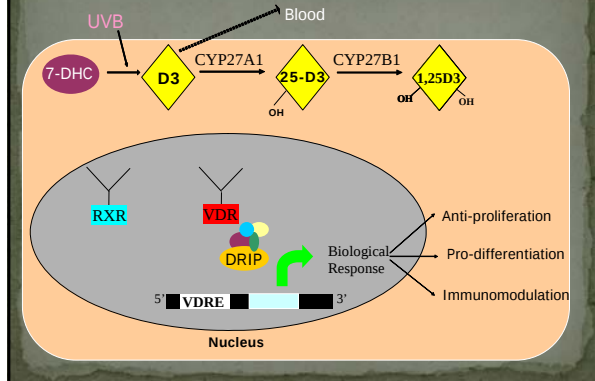


Vitamin D, Selenium and Chemoprevention of Prostate Cancer

Sebastiano Gattoni-Celli, M.D.
Department of Radiation Oncology
Medical University of South Carolina
Charleston VA Medical Center

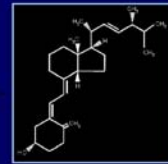


Vitamin D3 pathway in SKIN

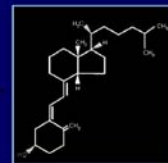


Types of Vitamin D

- Vitamin D₂**
- Formed by irradiation of ergocalciferol, found in plants
 - Provided by some dietary sources and multivitamins
 - Biologically inert
 - Conversion (OH) in liver and kidneys produces active form
 - D₂ is less potent than D₃

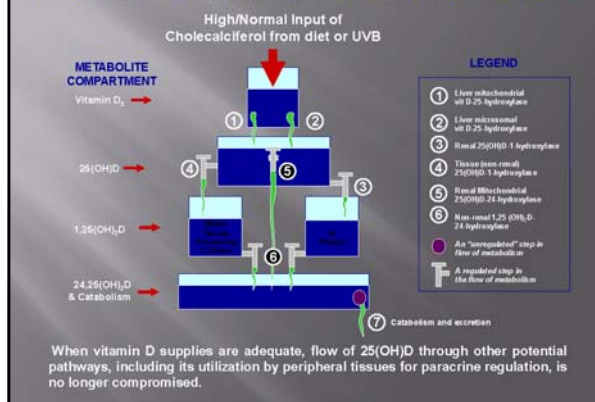


- Vitamin D₃**
- Naturally occurring form in humans
 - Formed by action of ultraviolet light on vitamin D precursors in skin
 - Present in certain nutrients
 - Biologically inert
 - Conversion (OH) in liver and kidneys produces active form

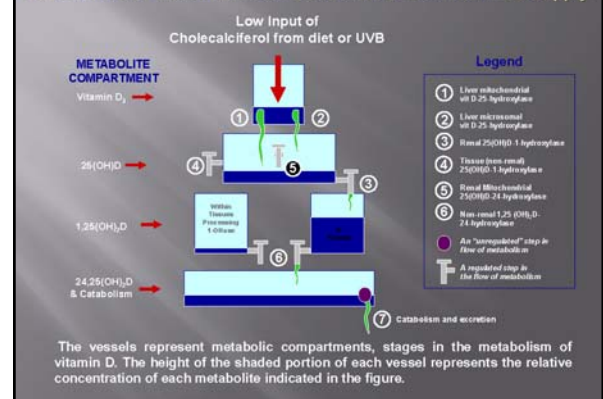


1. Parfitt AB et al. *Am J Clin Nutr*. 1982;36:1014-1021.
 2. Lips P. *Endocr Rev*. 2001;22:477-501.

Metabolism of Vitamin D Under Conditions of Adequate Vitamin D Supply



Metabolism of Vitamin D Under Conditions of Low Vitamin D Supply



A single initial MED dose of UVB radiation to a light-skinned individual will release approximately 20,000 IU vitamin D₃ into the circulation within 24 hrs.

However, if an individual has very dark skin the exposure time for a MED could increase by 10-fold.

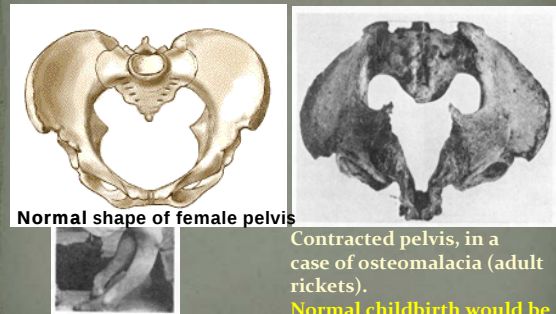
Number of months that UVB from sunshine cannot produce vitamin D₃ in skin



Vitamin D and Melanin

- SLC24A5 is a gene that controls melanin production
- This gene underwent a mutation around 6000 years ago, apparently at the time that hunter-gatherers, fishers, and herders became farmers
- Until then, their diet supplied enough vitamin D
- When farming spread in the last 6000 years, Europeans lost their ability to make melanin because they needed more vitamin D
- Heavier clothing might have also played a role
- Science, volume 316, page 364, 2007

Childhood lack of vitamin D causes rickets

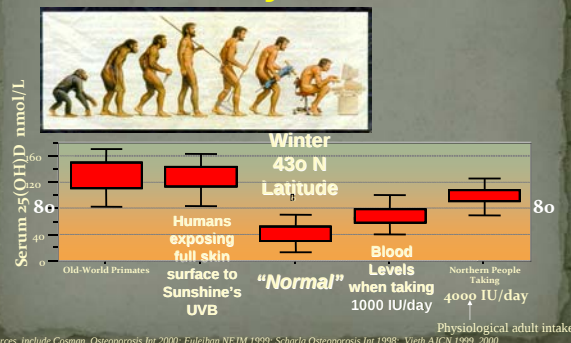


Normal shape of female pelvis

Contracted pelvis, in a case of osteomalacia (adult rickets).
Normal childbirth would be impossible.

Vieth 2001, Nutritional Aspects of Osteoporosis, Chapter 17, ed P. Burckhardt, RP. Heaney, B. Dawson-Hughes, Academic Press

Vitamin D Status in Primates and Early Humans

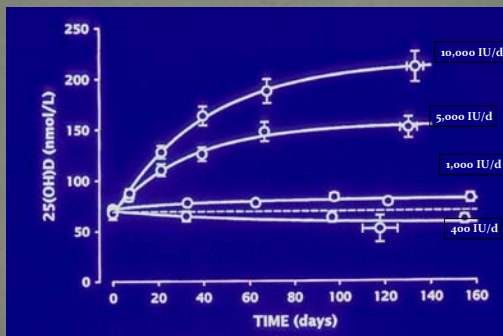


Sources: include Cozzman, Osteoporosis Int 2003; Falekhan NEJM 1999; Scharla Osteoporosis Int 1998; Vieth AJCN 1999, 2000

"Normal" Vitamin D Status

- Should NEVER have been defined by Gaussian distribution.
- This is similar to defining "normal" estrogen levels by sampling a population of women whom are primarily postmenopausal.

Circulating 25(OH)D₃ as a Function of Oral Vitamin D₃ Intake

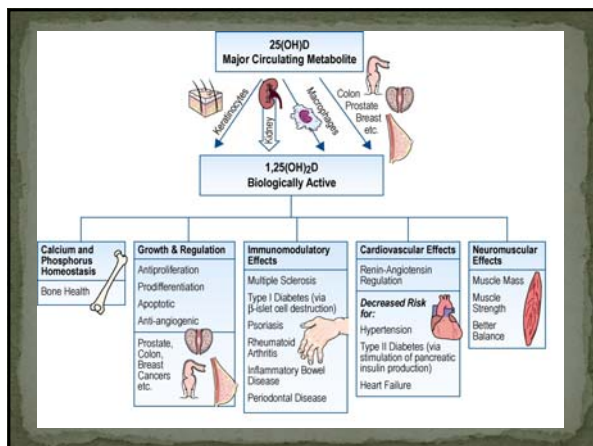
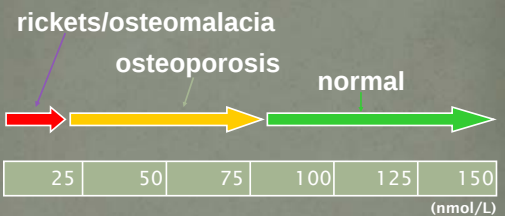


How toxic is vitamin D?

- The U.S. Nutrition Guidelines state that the lowest observed adverse effect level (LOAEL) for humans is 2,000 IU vitamin D/day
- This statement is grossly in error and is an impediment to the health of humans

However

- 1- hydroxylated vitamin D metabolites and analogues are extreme hypercalcemic agents!!!
- DO NOT CALL EVERYTHING VITAMIN D. 1,25(OH)₂D IS A HORMONE!!!!!!
- 1,25(OH)₂D can be a deadly hypercalcemic agent.



“Vitamin D controls T cell antigen receptor signaling and activation of human T cells.”

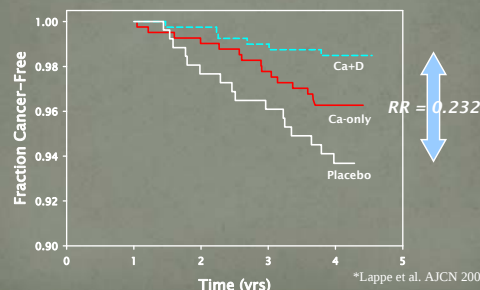
Rode von Essen et al. *Nature Immunology* 11:344-349, 2010

RCT for Vitamin D₃ Supplementation and Cancer

- 1179 healthy women
- aged 66.7 ± 7.3
- four year trial
- 1032 finished (87.5%)
- baseline 25(OH)D: $71.8 \text{ nmol/L} \pm 20.3$
- three treatment groups:
 - control
 - Ca (1400–1500 mg/d)
 - Ca plus D₃ (1100 IU/d)

*Lappe et al. AJCN 2007

VITAMIN D & CANCER*



Conclusions

- Based on biomarkers of nutritional vitamin D status (PTH, BMD, intestinal calcium absorption, insulin sensitivity, beta cell function, and innate immune function), circulating levels of 25(OH)D $<32 \text{ ng/mL}$ should be considered deficient.
- A 400 IU DRI for vitamin D is irrelevant with respect to the adult population in general.
- Guidelines stating that the lowest observed adverse effect level for humans is 2,000 IU vitamin D/day are incorrect. In actuality, the AI for adults may be 2,000 IU/day and in some cases, such as pregnancy and lactation, higher.
- It is not unlikely that chronic nutritional vitamin D deficiency puts populations at risk for developing debilitating, long latency chronic diseases such as cancer and autoimmune disease.
- Vitamin D probably plays a crucial role in cancer prevention.
- The physician will have to become familiar with vitamin D, not simply as a dietary supplement. **Active management of nutritional vitamin D status will become indispensable.**

Vitamin D and Prostate

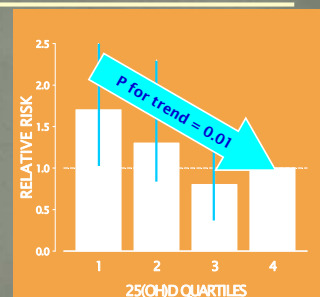
- Human prostate cells express the vitamin D receptor (VDR) and the androgen receptor (AR)
- Normal prostate cells also synthesize 1,25(OH)₂D₃ (calcitriol), which remains sequestered in the gland
- 1,25(OH)₂D₃ can inhibit the proliferation of prostate cancer cells both *in vitro* and *in vivo*, through AR-dependent and AR-independent mechanisms
- 1,25(OH)₂D₃ enhances AR expression and there is clear evidence of cross-talk between VDR and AR
- VDRE are present in regulatory regions of up to 10% of the human genome

Mechanisms of Action of Vitamin D

- Vitamin D induces the expression of insulin growth factor binding protein-3 (IGFBP-3), which increases the levels of the cell-cycle inhibitor p21
- Vitamin D represses the expression of COX-2, the key enzyme for the synthesis of prostaglandins, mediators of inflammation and thought to be important for cancer progression
- Vitamin D decreases matrix metalloproteinases and cathepsin activities, while increasing the activities of their counterparts, tissue inhibitors of metalloproteinase-1 and cathepsin inhibitors
- **Vitamin D can do a lot of other things because it can affect the expression of 2000 human genes**

Serum 25(OH)D₃ & Prostate Cancer

- 13 yr longitudinal study
- 19,000 men
- 149 cases prostate CA



Ahonen et al., Cancer Causes & Control 11, 847-852 (2000)

Design of Prospective Study

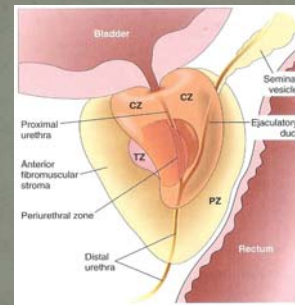
- Enroll 80 male subjects diagnosed with early-stage, low-risk PCa, a serum PSA value of ≤ 10.0 ng/ml, and a Gleason score of 6 or less (FDA IND 77,839)
- All subjects will have decided to be monitored through active surveillance for at least one year, before deciding whether or not to undergo definitive treatment (surgery and/or radiation therapy)
- Primary Objective: To test the hypothesis that a daily dose of vitamin D3 (4,000 IU) taken for 12 months will result in a decrease serum PSA levels in a significant number of enrolled subjects
- Secondary Objective: To compare prostate biopsy specimens (% positive cores) pre- and post-treatment

Visit	1	2	3	4	5	6	7	8
	Screening	Enrollment						Termination
Week	0	0	+8	+16	+24	+32	+40	+48
[Window]		+1-7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days
ICD	X							
Brief PE	X							X
BPHR	X		X	X	X	X	X	X
Past Medical History	X							
Inclusion/Exclusion Criteria	X	X						
Labwork:								
**BMP, *serum phosphorus	X		X	X	X	X	X	X
CBC w/diff	X		X	X	X	X	X	X
PSA	X		X	X	X	X	X	X
PTH	X		X	X	X	X	X	X
25(OH)D	X		X	X	X	X	X	X
*Urine CalCreat ratio	X		X	X	X	X	X	X
Food Frequency (FFQ)		X						
Adverse event		X	X	X	X	X	X	X
Concomitant med/supplements	X	X	X	X	X	X	X	X
Disperse study drug		X	X	X	X	X	X	
Med compliance			X	X	X	X	X	X
**Prostate Biopsy								

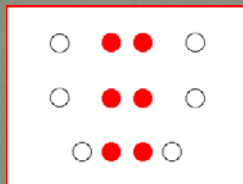
Current Status

- Forty five subjects have been enrolled thus far
- One subject was terminated because he was diagnosed with colorectal cancer shortly after enrollment; a second subject was taken off study because his PSA rose to >10 ng/mL serum; and a third subject was non-compliant
- No toxicity was observed or recorded with any of the subjects enrolled and treated thus far

Anatomy



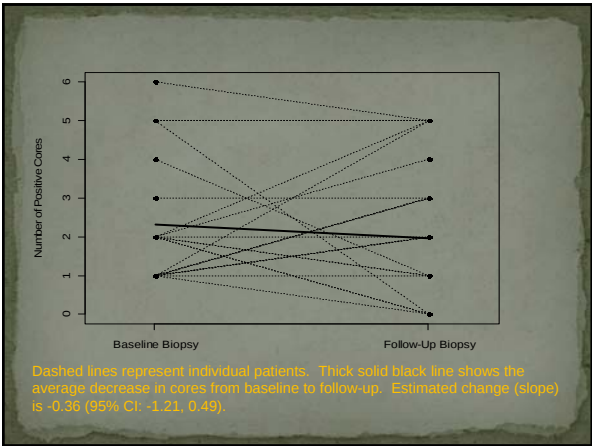
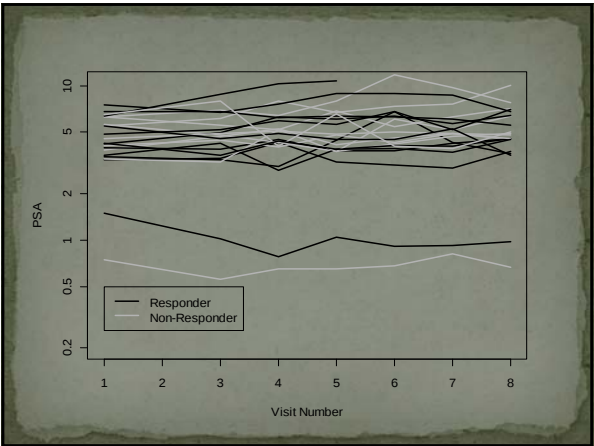
Diagnostic Work-Up



Prostate core biopsy schema Coronal prostate plane depicts a 12 core biopsy schema. Filled circles represent standard sextant sites, while open circles represent additional lateral sites within the gland for extended biopsies.

Subj # (race-age)	Pre-Study Results			Post-Study Results		
	25(OH)D	PSA	Bx: + cores (Total 12 cores)	25(OH)D	PSA	Bx: + cores (Total 12 cores)
2 (c-57)	57.69	3.46	1 (+2 PIN)	67.5	3.64	0
3 (c-63)	45.1	3.83	1	83.2	4.49	3 (+1 PIN)
4 (c-69)	12.6	3.98	4 (+1 PIN)	51.1	4.55	0 (+1 PIN)
6 (c-67)	32.3	3.33	6	63.3	3.76	5
8 (c-68)	17.1	5.65	2 (+1 PIN)	84.8	4.94	5
11 (c-57)	24.3	3.57	1	50.6	4.53	0
12 (c-65)	17.3	6.28	2	65.9	7.11	3
14 (c-69)	30.4	1.5	1	50.7	0.98	0
15 (c-69)	35.5	0.75	1	69.3	0.67	2
17 (c-62)	35.4	4.13	2	57.9	4.83	4
18 (aa-49)	25.5	3.37	2	70.1	6.37	3
19 (aa-68)	27	4.21	5	56	6.45	2
20 (aa-52)	28.5	5.48	3	51.7	10.1	4
22 (c-70)	75	4.56	1	84.1	4.55	2
23 (aa-70)	19.5	6.3	5	77.9	7.8	2*
24 (aa-65)	22.5	4.85	5	79.1	7.01	2
25 (aa-65)	29.2	6.38	2	48.2	10.8	1
26 (aa-58)	16.6	7.52	1	69.7	6.79	0 (+1 PIN)
28 (c-68)	39	6.77	2	73.8	5.59	0
29 (c-55)	37.2	5.49	1	95.4	3.55	0
30 (aa-71)	14.7	6.54	2	82.3	5.03	4 (+2 PIN)**
31 (aa-70)	12.3	4.25	1	90.2	4.47	1***

Bx: Biopsy; PIN: Prostatic Intraepithelial Neoplasia; * progression to Gleason 4+4 in one core; ** progression to Gleason 3+4 in four cores; ***50% positive core decreases to <5%.



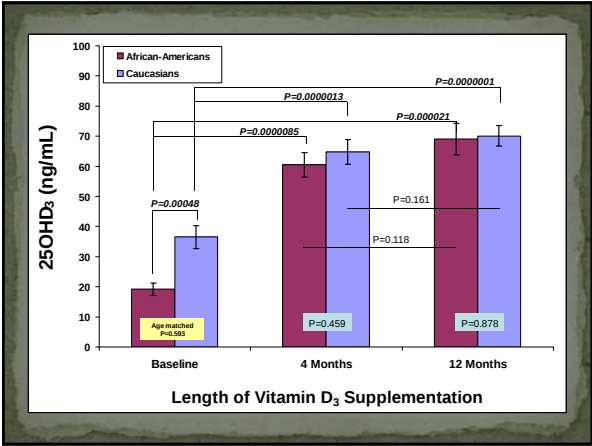
Vitamin D is beneficial for:

- CANCER (chemo-preventive)
- DIABETES (anti-inflammatory)
- HYPERTENSION (anti-inflammatory)
- ALZHEIMER'S DISEASE (?)

•THESE CONDITIONS ARE MORE PREVALENT IN THE AFRICAN-AMERICAN POPULATION

African-Americans		Caucasians	
Age, years	25OH-D, ng/mL	Age, years	25OH-D, ng/mL
50	10.6	50	23.1
51	19.1	50	34.3
51	31.4	51	22.4
52	24.5	51	44.7
53	15.9	52	22.4
53	21	53	24
53	34	53	24.7
54	14.3	54	30.3
54	14.5	55	50.1
54	20.5	56	25.2
55	14.5	57	20.4
56	6.9	57	30
56	11	57	56.9
56	11.9		
56	19.2		
57	12.1		
58	16.9		
60	9.1		
60	18.9		
62	24.6		
63	14.7		

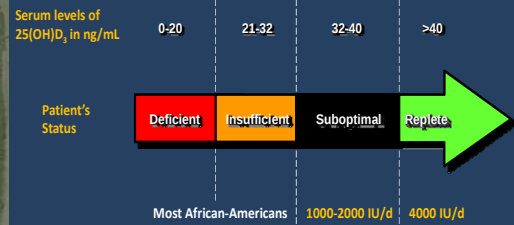
African Americans			Caucasians		
Age	Baseline 25OH-D	Exit 25OH-D	Age	Baseline 25OH-D	Exit 25OH-D
64.3±8.4			66±6.5		
49	25.5	70.1	54	37.2	95.4
52	28.5	51.7	57	57.6 +	67.5
58	16.6	69.7	57	24.3 +	50.6
			62	35.4	57.9
			62	35.7	78.1
			63	45.1 +	83.2
64	22.5 +	79.1	64	17.3	65.9
67	27	56	67	35.5 +	69.3
			67	39	73.8
			67	32.3 +	63.3
			68	12.6	51.1
			68	17.1	84.8
69	19.5	77.9	68	30.4 +	50.7
70	11.7	78.4	70	75 +	84.1
70	14.7	82.3	74	51.3 +	84.5
70	12.3	90.2	76	44.1	75.8
74	13.7	35.7	78	30.3 +	55.3
19.2±6.3			36.5±15.5		
69.1±16.6			70.1±13.9		



Adequate Intake of Vitamin D

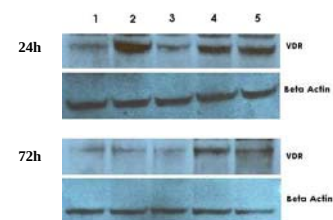
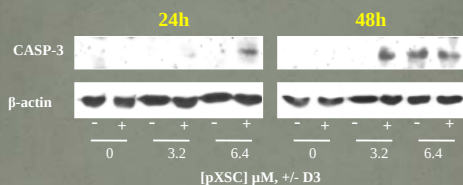
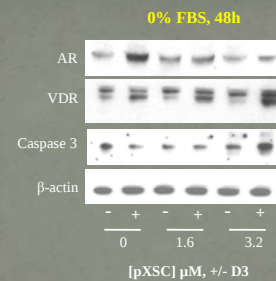
- The current recommended daily intake (RDI) is 400IU
- Vitamin D RDI is way too little for good health
- Melanin protects African-Americans from skin cancer; however, it prevents vitamin D production in the skin
- This can be remedied by supplementation
- The desirable level of vitamin D in blood is at least 40ng/mL**
- This can be easily achieved by taking 4000IU/day

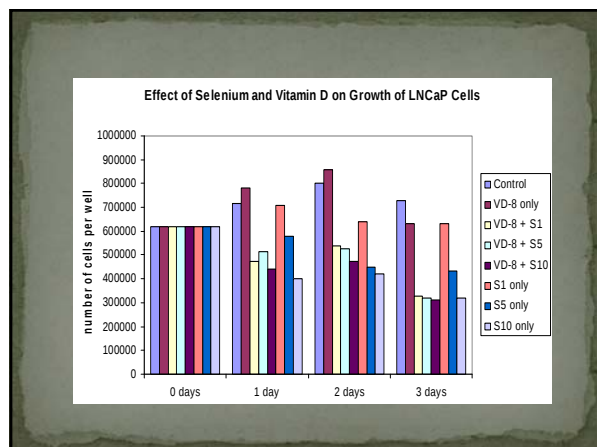
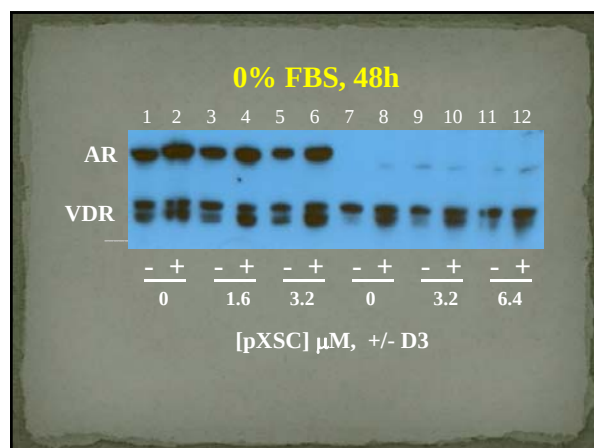
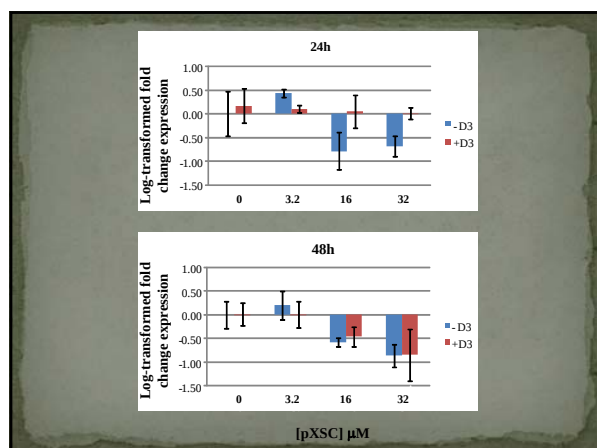
Circulating Levels of Vitamin D₃



SELENIUM and PROSTATE CANCER

- Chemo-preventive agent for prostate cancer (Clark, *JAMA*, 276:1957-1963, 1996)
- This randomized study was mostly conducted in Arizona and other sun-rich states, and was restricted to patients with a diagnosis of skin cancer (basal or squamous cell carcinoma)
- However, the Selenium and Vitamin E Cancer Prevention Trial – SELECT failed to confirm previous indications
- We investigated the interaction between vitamin D and selenium in LNCaP cells





- ### Preliminary Conclusions
- These preliminary observations support the use of 4,000 IU of vitamin D₃ as a chemopreventive/therapeutic agent, especially in men with early-stage, low-risk prostate cancer
 - The results of our *in vitro* studies suggest that combining vitamin D₃ and selenium supplementation may provide even more effective chemoprevention

- ### Acknowledgments
- David T. Marshall
 - Stephen J. Savage
 - Thomas E. Keane
 - Bruce W. Hollis
 - Elizabeth Garrett-Mayer
 - Linda H. Ambrose
 - Blake C. Ellis-Hays
 - Jin Yu
 - Mark S. Kindy
 - Supported by Gateway for Cancer Research and VA Merit Award

The (long, but fulfilling) Journey to a Dual-Degree

Gabrielle F. Cannick, DMD, PhD
June 23, 2010

Gabrielle's Timeline 2001-2009

Or:

What I did for 8 years at MUSC

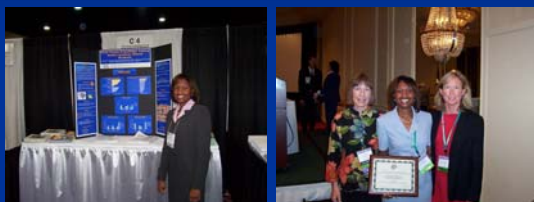
2001-2002 First Year of Dental School



2002-2003 Got Married Started Grad School



2003-2004 NIDCR/NIH



MUSC Oral Cancer Knowledge Among South Carolina Dental Students
Gabrielle F. Cannick, BS, Alice M. Horowitz, PhD, Thomas E. Drury, PhD, Susan G. Reed, DDS, DrPH, Terrence A. Day, MD

Abstract
Recent studies indicate that the highest oral cancer (OC) mortality rates are found in the Southeastern United States. However, little is known about the oral cancer knowledge of dental students in this region. The purpose of this study was to assess the oral cancer knowledge of dental students in South Carolina. A cross-sectional survey was conducted among 100 dental students at the University of South Carolina (USC) School of Dental Medicine. The survey included questions about OC risk factors, signs and symptoms, and screening methods. The results of the survey are presented in this abstract.

Background
Among the five states, South Carolina has the highest oral cancer mortality rate, second only to the District of Columbia. Therefore, it is important that South Carolina dental students acquire current knowledge on the state of oral cancer.

Objectives
To determine the oral cancer knowledge of dental students in South Carolina and to assess the relationship between oral cancer knowledge and OC mortality.

Methods
A cross-sectional survey was conducted among 100 dental students at the USC School of Dental Medicine. The survey included questions about OC risk factors, signs and symptoms, and screening methods. The results of the survey are presented in this abstract.

Results
The survey results are presented in this abstract. The results show that dental students in South Carolina have a good understanding of OC risk factors and signs and symptoms, but they need more information about screening methods. The results also show that dental students in South Carolina have a good understanding of the relationship between oral cancer knowledge and OC mortality.

Conclusions
The results of this study indicate that dental students in South Carolina have a good understanding of OC risk factors and signs and symptoms, but they need more information about screening methods. The results also show that dental students in South Carolina have a good understanding of the relationship between oral cancer knowledge and OC mortality.

Oral Cancer Examination
The Oral Cancer Examination is a new examination for dental students. It is a multiple-choice examination that tests the student's knowledge of oral cancer. The examination is designed to assess the student's knowledge of oral cancer risk factors, signs and symptoms, and screening methods. The examination is a valuable tool for assessing the student's knowledge of oral cancer.

2004-2006
Dissertation/Life



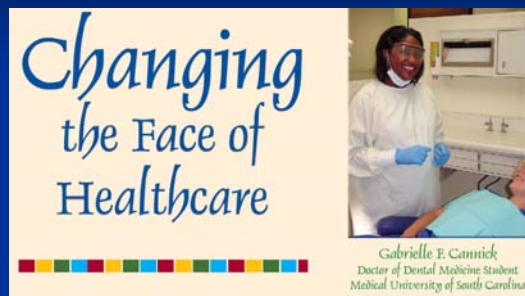
2006-2007
Returned to Dental School



2007-2009
Family/Dental School



2009
Finally done!



Drs. Sparkle Pompey and Gabrielle Cannick



So glad to be finished!



And the newest addition....



Awards, Presentations, and Publications

Awards

Individual Predoctoral Dentist Scientist Fellowship, NIDCR F30DE017046 (2008-2009)

APHIA Anthony Westraizer-Jong Memorial Community Dental Public Health Professional Award (2006)

Quantitative Award for Clinical Achievement in Dental Research, College of Dental Medicine, Medical University of South Carolina, May 14, 2009

The Charleston Dental Society Scholar Award, Charleston Dental Society, May 14, 2009

Presentations

Canack, G.F., AM Horowitz, DR Garr, BW Neville, SG Reed, RF Woodson, TA Day, and DT Lackland. Use of PRECEDE-PROCEED to develop an oral cancer prevention and detection curriculum. Second North American Congress of Epidemiology, Seattle, June 21-24, 2006. Poster Presentation.

Canack, G.F., AM Horowitz, DR Garr, BW Neville, SG Reed, TA Day, and DT Lackland. A model for change: oral cancer in the dental school curriculum. National Oral Health Conference, Little Rock, May 1-3, 2006. Roundtable Presentation.

Canack, G.F. Development and implementation of an oral cancer educational program for dental students. American Public Health Association 130th Annual Meeting, Philadelphia, December 10-14, 2005. Invited Oral Presentation.

Canack, G.F. and DT Lackland. Development and implementation of an oral cancer educational program for dental students. Medical University of South Carolina Student Research Day, Charleston, November 8, 2005. Poster Presentation.

Publications

Canack, G.F.1,2, A.M. Horowitz2, T.F. Dyer2, S.G. Reed3, T.A. Day4, Department of Biometrics and Epidemiology, College of Graduate Studies, and College of Dental Medicine, Medical University of South Carolina (MUSC); 2 National Institute of Dental and Craniofacial Research, National Institutes of Health; 3 Department of Stomatology, College of Dental Medicine, MUSC; 4 Department of Otorhinolaryngology-Head and Neck Surgery, MUSC. Assessing oral cancer knowledge among dental students in South Carolina. *Journal of the American Dental Association*. 2005;136:773-4.

Canack, G.F.1, A.M. Horowitz2, S.G. Reed3, T.F. Dyer2, T.A. Day3, Department of Stomatology and Department of Biometrics, Biostatistics, and Epidemiology, Medical University of South Carolina (MUSC); 2 National Institute of Dental and Craniofacial Research, National Institutes of Health; 3 Department of Otorhinolaryngology-Head and Neck Surgery, MUSC. Opinions of South Carolina Dental Students toward Tobacco Use Interventions. *Journal of Public Health Dentistry*. 2006;66(1):44-8.

Canack G.F., Horowitz AM, Garr DR, Reed SG, Neville BW, Day TA, Woodson RF, Lackland DT. Oral Cancer Prevention and Early Detection: Using the PRECEDE-PROCEED framework to guide the training of health professional students. *Journal of Cancer Education* 2007;22(6):290-3.

Canack G.F., Horowitz AM, Garr DR, Reed SG, Neville BW, Day TA, Woodson RF, Lackland DT. Use of the OCE to evaluate brief communication skills training for dental students. *Journal of Dental Education* 2007;71(9):1210-3.

Mishra A, Oh A, Akhtar A, Canack G, Ford M, Carpenter M, Miller P, Sathyanarayana N, Day T. Head and Neck Cancer Prevention (2010). In S.C. Yang and W.M. Koch (Eds.), *Early Diagnosis and Treatment of Cancer Head and Neck Cancer* (pp. 107-199). Philadelphia: Saunders/Elsevier.

Introduction to Radiation Oncology

Leander Cannick

What is Radiation Oncology?

- Treatment of various conditions with X-Ray therapy
- Part of the usual triad of cancer treatments surgery, chemotherapy, and radiation

Intro to the Lingo Units of Radiation

- Gray (Gy)
 - SI unit absorbed dose
 - Old unit was the rad
 - $1\text{cGy} = 1\text{rad}$

External Beam Radiation Therapy (EBRT)

- X-ray or photon treatments are delivered by linear accelerators
- Mega-voltage x-rays can penetrate deeper to treat the tumor
- For curative cancers, once daily treatments are usually given in an outpatient setting for about 6-8 weeks
- Radiation can be given palliatively for 2-3 weeks

Why Do We Fractionate Radiation Dose?

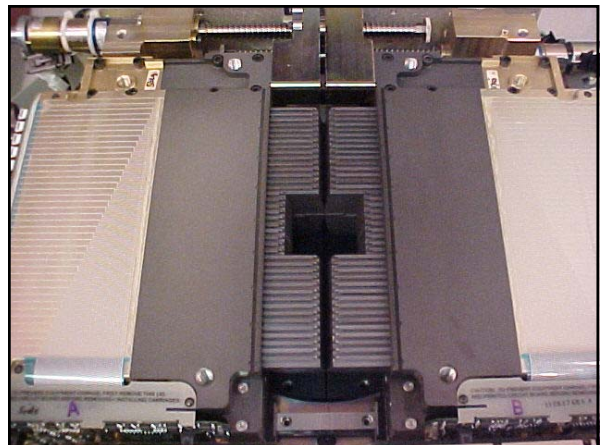
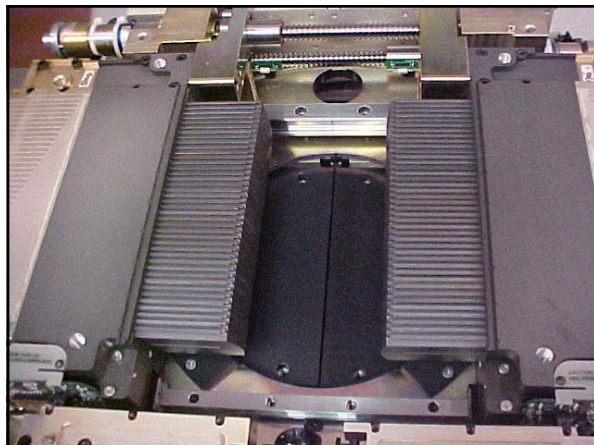
- Cannot treat tumor in isolation without treating some surrounding normal tissue
- Therapeutic benefit
 - When radiotherapy is given in small doses daily, normal tissue has a greater capacity to repair than to tumor cells

Why Do We Fractionate Radiation Dose?

Fractionation



Linear Accelerators

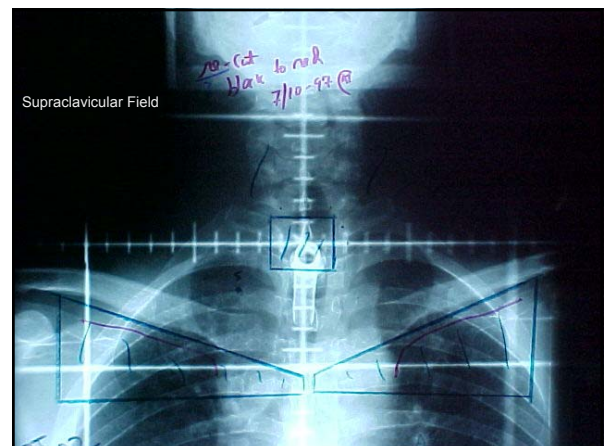
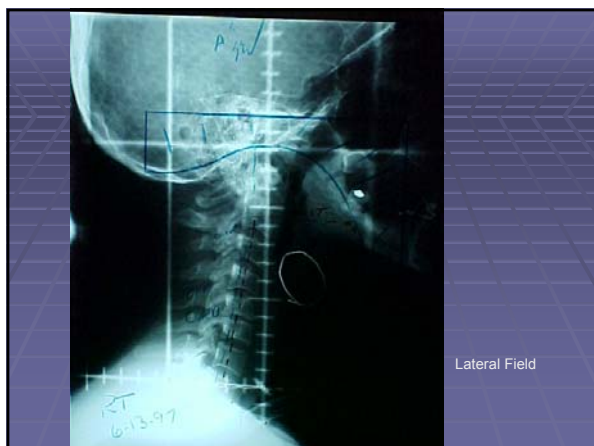
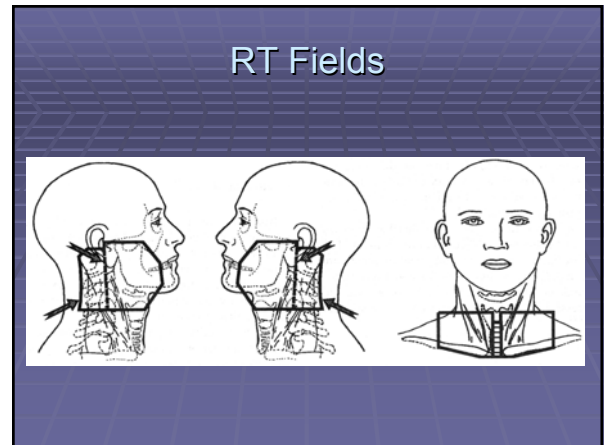
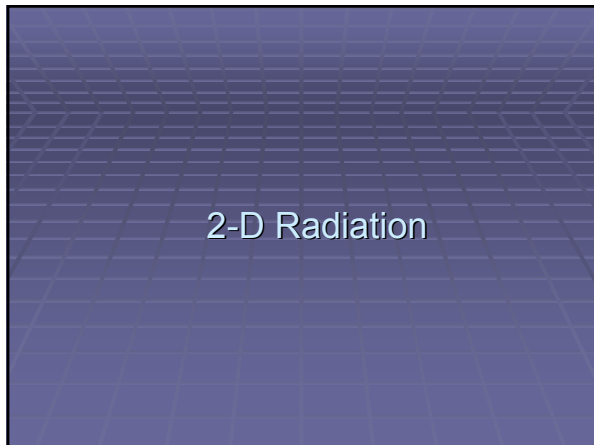


Immobilization

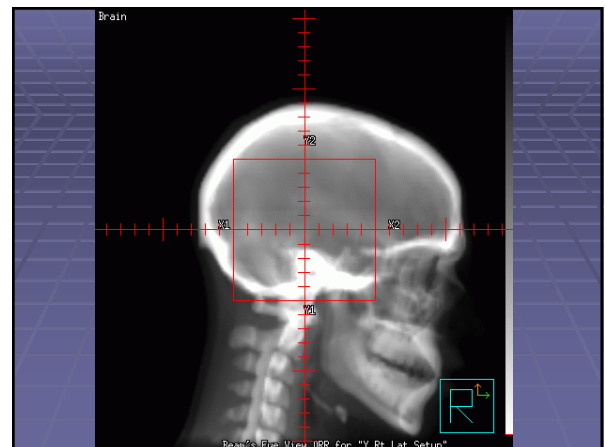
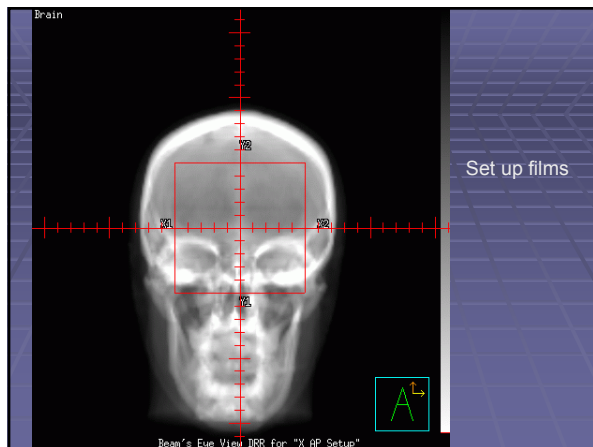
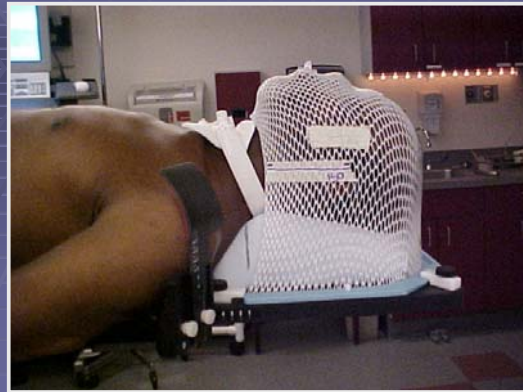


Keloids

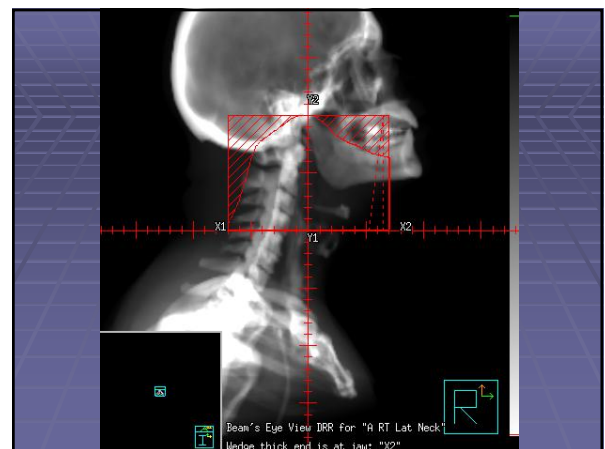


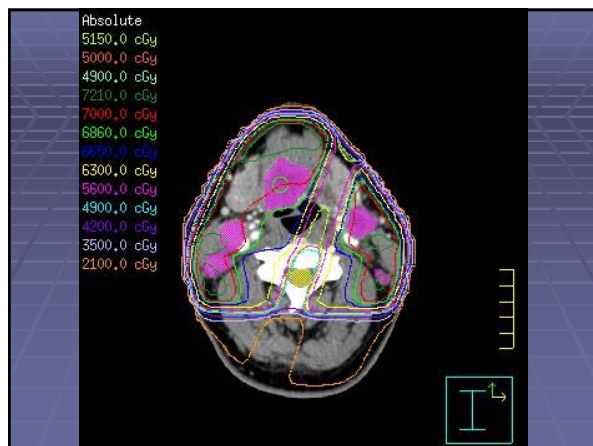
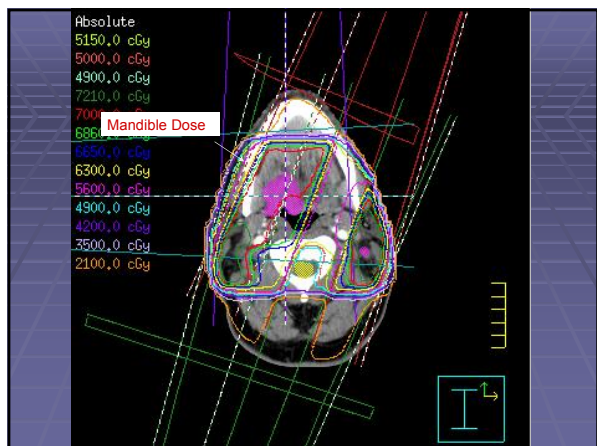
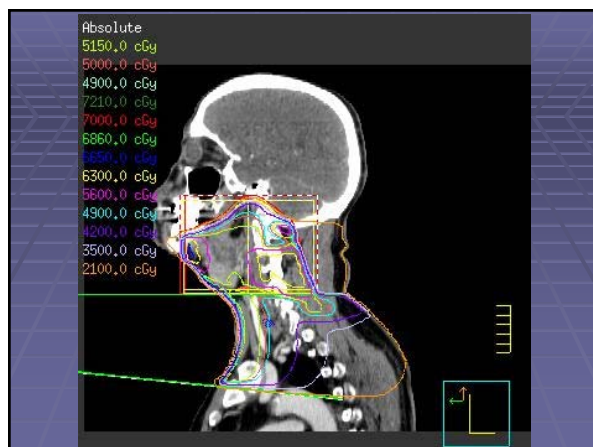
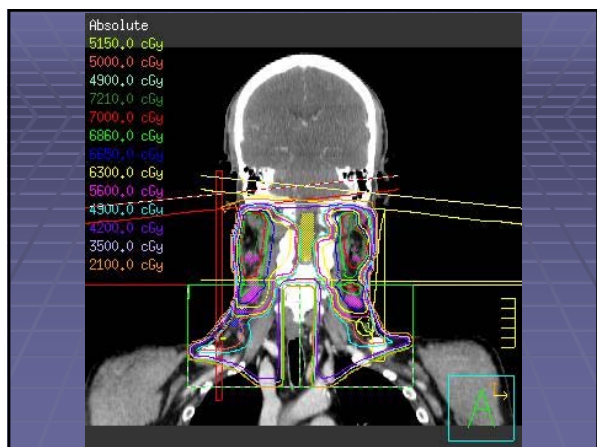
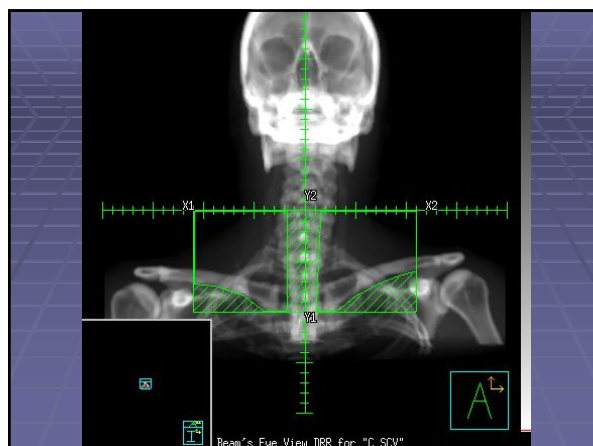
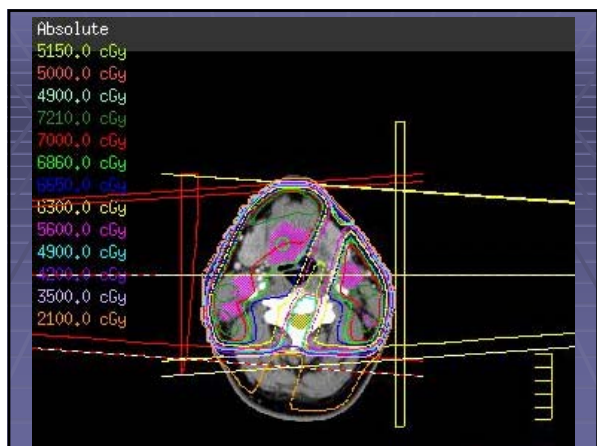


3-D Radiation



3-D RT Treatment for Right Base of Tongue Lesion

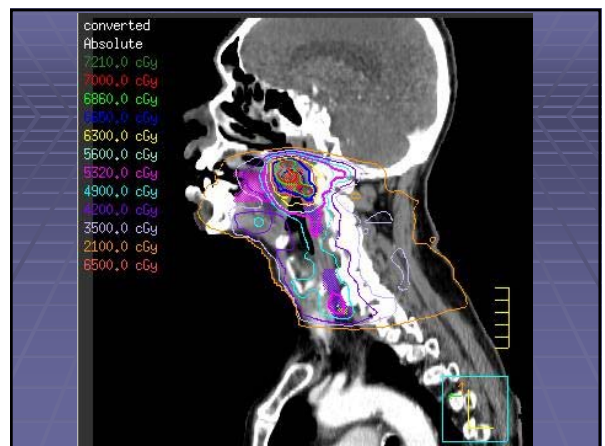
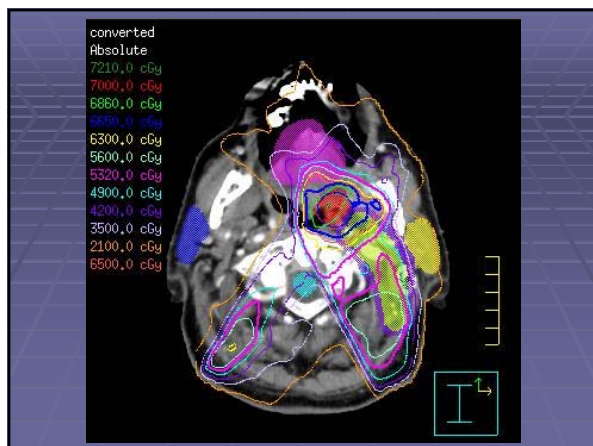
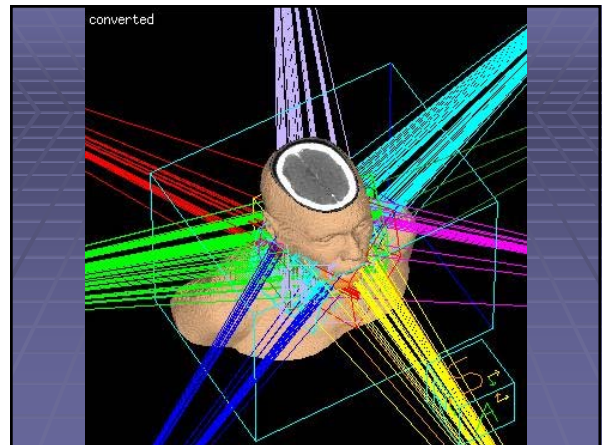


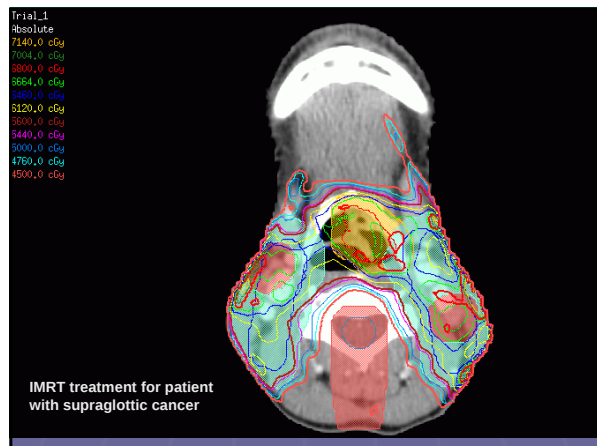


IMRT (Intensity Modulated Radiation Therapy)



IMRT Treatment for Tonsillar Cancer





Toxicities of HNC Treatments

- Fatigue
- Edema of soft tissues
- Oral Mucositis
 - Radiation induced
 - Chemotherapy induced
- Skin erythema and desquamation
- Xerostomia

Oral Mucositis (OM)

- OM generally develops within 2 weeks after the beginning of radiation but may start earlier if chemotherapy is given concurrently.
 - Turnover rate of the epithelial cells of the oral mucosa is ~ 2 weeks and that is the approximate time that it takes for OM to manifest.
- Any of the oral mucosae can be the site of OM but preferentially those that do not keratinize such as lips, buccal, soft palate, ventral tongue and pharyngeal mucosae.

Oral Mucositis

- Different stages of OM
 - Grade I: Erythema
 - Grade II: Erythema with patchy ulceration
 - Grade III: Erythema with confluent ulceration



Skin Toxicity

- RTOG acute morbidity scoring scale
 - **Grade 0:** No changes
 - **Grade 1:** Follicular, faint or dull erythema/ epilation/dry desquamation/ decreased sweating
 - **Grade 2:** Tender or bright erythema, patchy moist desquamation/ moderate edema
 - **Grade 3:** Confluent, moist desquamation other than skin folds, pitting edema
 - **Grade 4:** Ulceration, hemorrhage, necrosis

Xerostomia

- **Grade I**
 - Mild mouth dryness with some altered taste and slightly thickened saliva
 - No alteration in eating behavior
- **Grade II**
 - Moderate to severe dryness with markedly altered taste
 - Diet is altered
- **Grade IV**
 - Necrosis of salivary gland

Xerostomia



This 60 year-old woman had undergone radiation for an adenocarcinoma of the parotid gland. Note the rampant caries and the dryness of the gingiva as a consequence to xerostomia.

Pros and Cons of RT as a career

1. Part of a team that helps to care for cancer patients
 2. Exciting and changing technology
 3. Able to work with surgeons and medical oncologists
 4. Good lifestyle
-
1. Many treatments are palliative
 2. Competitive to obtain a residency position
 3. Must keep abreast with the changing technology and treatment options.

Experimental Therapies for Prostate Cancer

Christina Voelkel-Johnson, Ph.D.

Department of Microbiology & Immunology
Cancer Immunology & Immunotherapy

Prostate Cancer

- 192,280 new cases (2009)
- 27,360 deaths (2009)
- ~85% localized at diagnosis
- Slow growing, 5yr survival > 90%
- AA>caucasian>hispanic>asian>NA
- Mortality in AA=75%
- 1/6 males affected
- Standard Treatment
 - Localized: radiation, surgery, watchful waiting
 - Advanced: hormone ablation (cancer becomes castration resistant)
 - Metastatic: chemotherapy (not curative, mostly palliative)
- Experimental Therapies
 - Gene Therapy
 - Immunotherapy

(Suicide) Gene Therapy

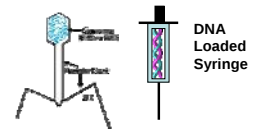
- Gene therapy is a technique for correcting defective genes responsible for disease development
- Suicide gene therapy involves a gene that when expressed leads to death of the infected cell
- The most common vector is a virus, since viruses have naturally evolved to infect human cells and deliver their genetic material
- Scientists manipulate the virus and insert a gene of interest to correct disease

http://www.ornl.gov/sci/techresources/Human_Genome/medicine/genetherapy.shtml

Infectious Viruses: A Genetic “Syringe”

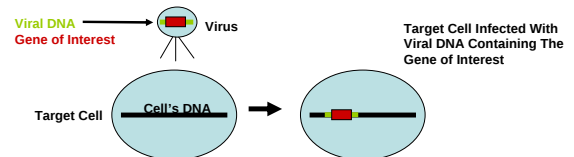
Viruses are composed of genetic material encapsulated in a protein coat.

Viruses inject their genetic material into target cells.



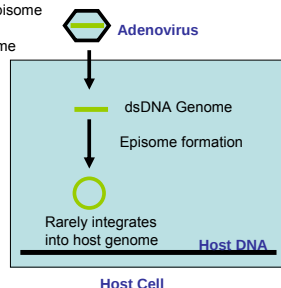
Viruses infect target cells with their genetic material.

The viral DNA can be altered to contain a gene of interest (rDNA) to infect that gene into the target cell.



Adenovirus

- dsDNA genome
- Non-Lipid Enveloped
- Upon infection, the viral DNA forms an episome
- Episome rarely integrates into host genome
- Fixed host range affecting Rodents, humans and other animals
- Known receptors: Coxsackie & Adenovirus Receptor (CAR) HLA / MHC I

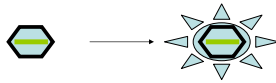


Obstacles

- Entry of adenovirus
 - via receptor
- Tropism of adenovirus
 - Liver and lungs
- Neutralization by the immune system
 - Pre-existing antibodies

Nanoparticle Shielding

- Coating the virus to hide it from pre-existing immunity
 - Polymer-Adenovirus Hybrids (PICs)
- Targeting the virus to cancer cells to overcome tropism
 - Conjugating an antibody to the PICs

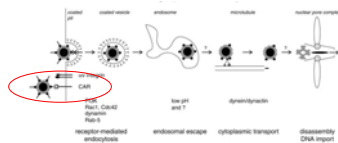


Obstacles

- Entry of adenovirus
 - via receptor
- Tropism of adenovirus
 - Liver and lungs
- Neutralization by the immune system
 - Pre-existing antibodies

Adenoviral Entry

Entry of adenovirus
via receptor



CAR - originally discovered as a viral receptor
but later found to be an adhesion molecule
Do cancer cells adhere?

Question

Do prostate cancer cells adhere?

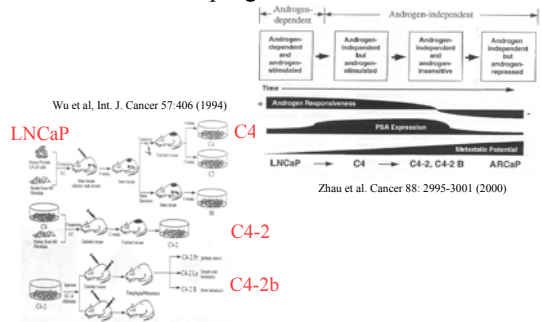
Downregulation of adhesion proteins is a
prerequisite for the ability to metastasize

CAR decreases in prostate cancer with
increasing tumor stage and grade

Research Questions

1. Is there a model that simulates this decrease in CAR?
2. Can we use this model to test how CAR expression affects adenoviral entry?
3. What can be done to increase adenoviral entry?

The LNCaP progression model of PC

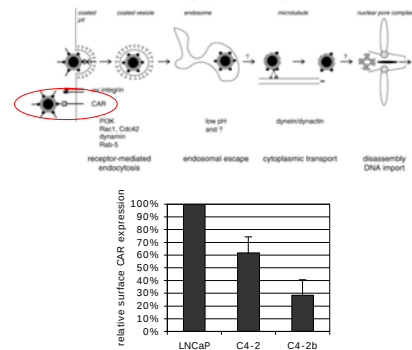


Flow cytometry

- Expression of proteins on the cell surface
 - Here: How much CAR is on LNCaP vs. C4-2b?
- Expression of reporter proteins
 - Here: we used GFP as a reporter to determine how many cells are infected by the adenovirus and how much of the transgene is expressed

http://probes.invitrogen.com/resources/education/tutorials/4Intro_Flow/player.html

Adenoviral entry and CAR



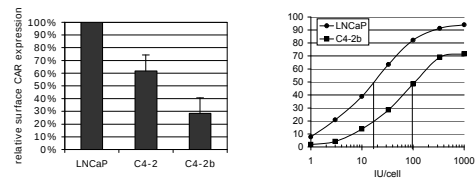
Questions

Is there a model that simulates this decrease in CAR? **YES**

Can we use this model to test how CAR expression affects adenoviral entry?

What can be done to increase adenoviral entry?

Adenoviral entry and CAR



Questions

Is there a model that simulates this decrease in CAR? **YES**

Can we use this model to test how CAR expression affects adenoviral entry? **YES**

What can be done to increase adenoviral entry?

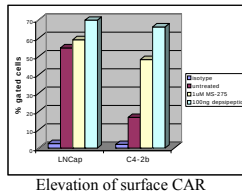
CAR and HDACi

- a novel class of chemotherapeutic drugs called histone deacetylase inhibitors (HDACi)

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

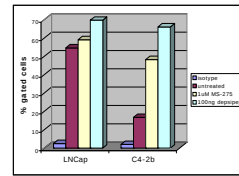
- In clinical trials for prostate cancer
- Increase CAR expression in bladder cancer
- Can HDACi increase CAR expression in prostate cancer cells?

HDACi restore CAR

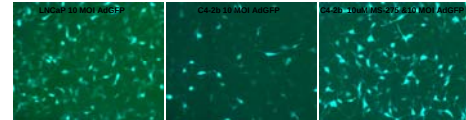
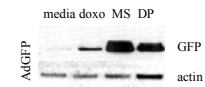


Elevation of surface CAR

HDACi increase infectivity



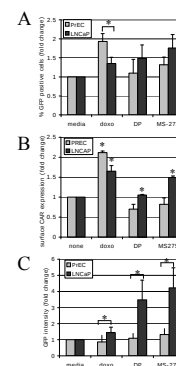
Elevation of surface CAR



Increased adenoviral infectivity and gene expression

Selectivity

- The goal of any cancer therapy is to selectively kill tumor cells
- HDACi can be safely administered to cancer patients with lower side effects than other drugs
- Can HDACi increase adenoviral infection selectively in tumor cells?



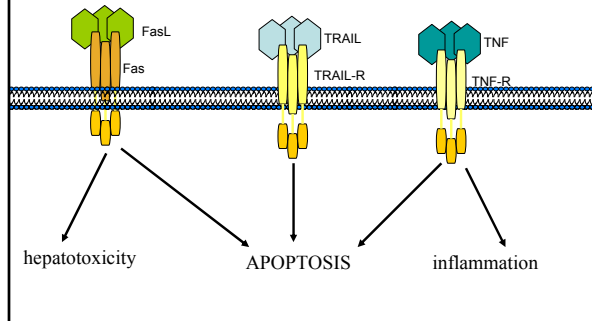
Conclusions-part 1

- Decreased expression of the adenoviral receptor CAR impairs adenoviral gene delivery
- HDACi restore CAR expression, increase adenoviral infectivity and gene expression
- HDACi exhibit selectivity for cancer cells

Research Question

- What therapeutic gene should be inserted into the adenovirus?
 - Gene should be able to kill cancer cells
 - Gene should NOT kill normal cells

Death Ligands as Cancer Therapeutics



TRAIL

(TNF Related Apoptosis Inducing Ligand /Apo2L)

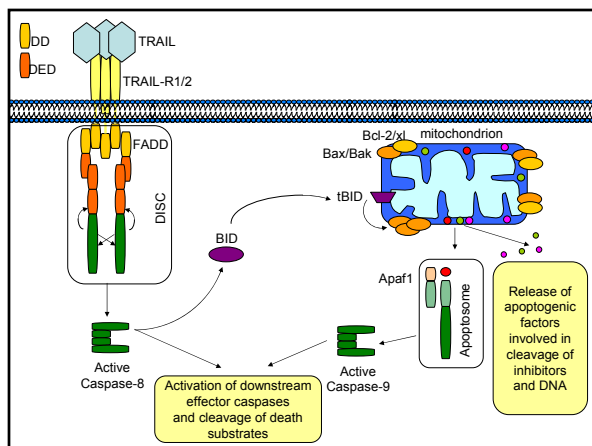
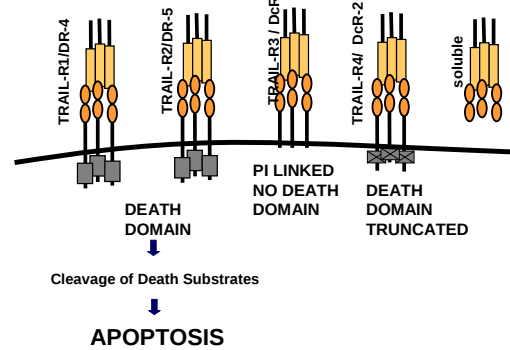
- discovered by 2 groups (Genentech/Immunex) 1995/1996
- member of the TNF superfamily (highest homology to FasL)
- Induces apoptosis in a variety of cancer cell lines
- Does not induce apoptosis in normal cells
- Preclinical studies confirmed safety of single agent therapy
- Clinical trials with rTRAIL and agonistic Ab against receptors ongoing

TRAIL

(TNF Related Apoptosis Inducing Ligand /Apo2L)

- TRAIL is expressed on a variety of activated immune cells
- TRAIL knockout mice are more susceptible to carcinogen-induced tumors
- Aging TRAIL knockout mice develop tumors of hematopoietic origin more frequently than controls
- BCG immunotherapy induces TRAIL release from neutrophils-correlates with treatment response

TRAIL Receptors



Status of TRAIL therapy

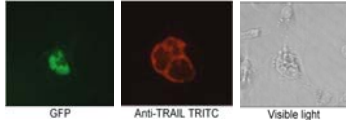
- Preclinical studies
 - Human tumor xenografts in mice (efficacy)
 - Non-human primates (safety)
- Clinical trials
 - Phase 1A: 39 patients, no response, no adverse effects
 - Phase 1A: 31 patients, 1 PR, 5 SD, no adverse effects
 - Phase 1: 51 patients, 1 PR, 13 SD, adverse effects included fatigue, headache, fever, vomiting, nausea, anemia, weightloss
 - pharmacokinetic assessment in 37 patients with 0.5-15 mg/kg rTRAIL revealed that serum concentration similar to xenograft studies can be safely achieved in humans.

Issue: short half-life of rTRAIL in circulation

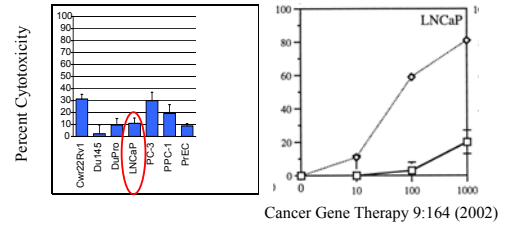
Gene Therapy using TRAIL



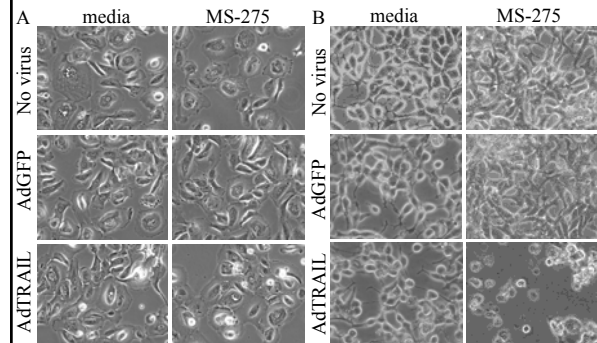
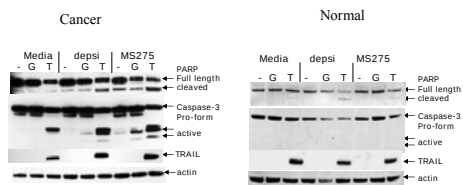
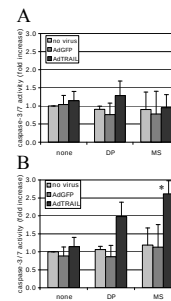
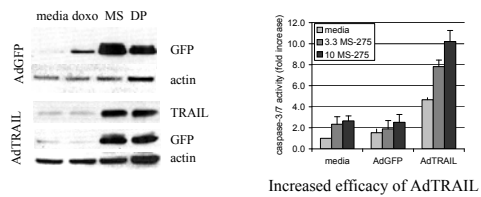
- Full-length TRAIL (membrane bound form)
- IRES allows translation of two proteins from one mRNA
- GFP as marker for infected cells



AdTRAIL can kill cells resistant to rTRAIL



HDACi increases efficacy of AdTRAIL



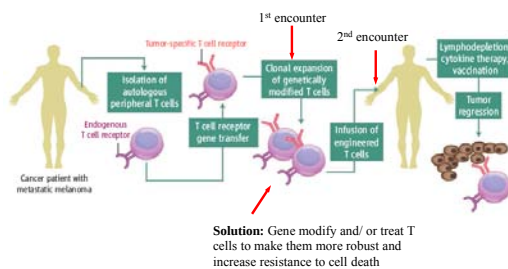
AdTRAIL trial

- Clinical trial has been conducted
- Patients - scheduled for prostatectomy
- Route - intra-prostatic injection
- Outcome measures - apoptosis

Conclusions

- AdTRAIL is more effective than rTRAIL
- Decreased expression of the adenoviral receptor CAR impairs adenoviral gene delivery
- HDACi SELECTIVELY restore CAR expression, increase adenoviral infectivity and gene expression, and improve efficacy in vitro

Immunotherapy Adoptive T cell transfer and AICD



Thank you!

Biostatistics in Prostate Cancer Research

Elizabeth Garrett-Mayer, PhD
Associate Professor of Biostatistics and Epidemiology
Director of Biostatistics, Hollings Cancer Center

July 1, 2010

DOD HBCU Collaborative Summer Undergraduate Research
Program: Prostate Cancer Research Training Curriculum

1

Statistics

- Statistics is the art/science of **summarizing data** and **quantifying evidence**
- Better yet...summarizing data so that non-statisticians can understand it
- Scientific investigations usually involve collecting a lot of data.
- But, at the end of your study, what you really want is a "punch-line:"
 - Did the new treatment work?
 - Are the two groups being compared the same or different?
 - Is the new method more precise than the old method?
- Statistical inference is the answer!

DOD HBCU Collaborative Summer Undergraduate Research
Program: Prostate Cancer Research Training Curriculum

2

How do statisticians help research?

- Statistics should be a part of the study from the very beginning
- Statistical issues arise in:
 - Study Design
 - Analysis
 - Interpretation of results
 - Conclusions

DOD HBCU Collaborative Summer Undergraduate Research
Program: Prostate Cancer Research Training Curriculum

3

What we do

- We plan
- We estimate
- We test

DOD HBCU Collaborative Summer Undergraduate Research
Program: Prostate Cancer Research Training Curriculum

4

What we do

- We plan
 - we help to plan clinical trials and other kinds of studies
 - we help figure out how many people to study
- We estimate
 - we determine what the "response rate" was
 - we estimate how much better treatment A is than treatment B
- We test
 - we determine which treatment is better
 - we quantify how much better using a test.

DOD HBCU Collaborative Summer Undergraduate Research
Program: Prostate Cancer Research Training Curriculum

5

Clinical Research in Prostate Cancer

- Research requires a plan
- A DETAILED plan called a "clinical trial protocol"
 - could also be an intervention
 - could also be an observational study
 - but, for simplicity, we focus on a "treatment trial"
 - Example: Velcade for treatment of men with relapsed prostate cancer

DOD HBCU Collaborative Summer Undergraduate Research
Program: Prostate Cancer Research Training Curriculum

6

Clinical Trial Protocol

- Variety of templates
- Some key elements
 - Specific Aims: you must state what your goals are in terms of measurable objectives
 - Background/Rationale: explanation of why this study is important, what preliminary data exists and justification of the dose.
 - Experimental Design: Describes how the study will proceed. no detail can be spared. someone else should be able to implement the study with no questions.
 - Analysis Plan: how will the data will handled and objectives answered.

DOD HBCU Collaborative Summer Undergraduate Research
Program: Prostate Cancer Research Training Curriculum

7

Clinical Drug Trial Checklist.

- 1 Study Title
- 2 Study personnel
- 3 Rationale
- 4 Objectives
- 5 Study Plan & Schedule of Assessments
 - 5.1 Methods of collecting data
 - 5.2 Study Plan
 - 5.3 Schedule of Assessments
- 6 Inclusion Criteria
- 7 Exclusion Criteria
- 8 Prohibited Drugs and Interventions.
- 9 Study design and analysis
 - 9.1 Randomisation
 - 9.2 Power calculations
 - 9.3 Data to be analysed
 - 9.4 Analysis populations
 - 9.5 Withdrawals (protocol violations, broken blinding, withdrawal)
 - 9.6 Statistical Analysis
 - 9.7 Interim analyses
- 10 Safety: Reporting of Adverse Events
 - 10.1 Definition of adverse events provided
 - 10.2 Investigator's responsibility to report adverse events
 - 10.3 Definition of serious adverse events in accordance with standard criteria
 - 10.4 Investigator's responsibility to follow-up and characterise adverse events
 - 10.5 Procedures for informing CDTC/RIEC of adverse events reports
- 11 Pharmacy issues: drug storage, dispensing and labelling
- 12 Administrative issues
- 13 Compliance With Good Clinical Practice, Ethical Considerations & Informed Consent

DOD HBCU Collaborative Summer Undergraduate Research
Program: Prostate Cancer Research Training Curriculum

8

Endpoint selection

- What measures should we take to determine if our treatment (e.g. Velcade) has worked?
- Example: for each patient, determine if his disease has
 - regressed (i.e., responded)?
 - stayed the same? ('stable disease')
 - progressed?
- Common endpoints in prostate cancer clinical trials
 - PSA (prostate specific antigen), a biomarker
 - tumor size/volume
 - pain
 - quality of life
- It is important to use endpoints that everyone else uses.

DOD HBCU Collaborative Summer Undergraduate Research
Program: Prostate Cancer Research Training Curriculum

9

Statistical Design Issues

- Choose most efficient design
- Consider all aims of the study
- Particular designs that might be useful
 - Cross-over
 - Pre-post
 - Factorial
- Sample size considerations
- Interim monitoring plan

DOD HBCU Collaborative Summer Undergraduate Research
Program: Prostate Cancer Research Training Curriculum

10

Example: prostate cancer clinical trial

- TAX327: Aventis study
- Patient Population: *hormone refractory metastatic prostate cancer*
- Large randomized clinical trial
 - docetaxel, schedule 1
 - docetaxel, schedule 2
 - mitoxantrone
- Primary endpoint: overall survival
- Additional Aim: how is PSA related to overall survival?
 - prostate specific antigen
 - well-known 'surrogate' for prostate cancer presence
 - well-known 'test' for prostate cancer progression
- Additional Aim: compare quality of life in the three treatment arms

DOD HBCU Collaborative Summer Undergraduate Research
Program: Prostate Cancer Research Training Curriculum

11

Study design

- Patients are randomized to one of three arms
- Equal chance of assignment to each arm
- Overall survival:
 - Time from randomization until death
 - Patients are followed until death
 - For patients who do not die by study end, we say that their outcomes are 'censored' at the last known time they were still alive (more on that later)
- Statistician worked with the clinicians to determine how many patients were needed
 - depends on how certain we want to be about our conclusion
 - the expected survival in each group
 - how long patients are followed
 - how long it takes to enroll patients

DOD HBCU Collaborative Summer Undergraduate Research
Program: Prostate Cancer Research Training Curriculum

12

Analysis Plan: Part of the Design!

- Statistical method for **EACH** aim
- Account for type I and type II errors
 - these quantify how certain we want to be about making mistakes
 - type I: the probability of concluding that there is a difference in treatments when there truly is no difference
 - type II: the probability of concluding that there is no difference when there truly is a difference
- Stratifications or adjustments are included if necessary
- Simpler is often better
- Loss to follow-up: plan for missing data

DOD HBCU Collaborative Summer Undergraduate Research
Program: Prostate Cancer Research Training Curriculum

13

Estimation

- At the end of the study, you need to be able to “measure” how things went
- Some examples:
 - what proportion of patients responded to the treatment?
 - how many patients are still alive at 5 years?
 - what is the difference in the response rate between the two treatment groups?
 - how much improvement was seen in quality of life from the beginning of the study to the end?
- Estimation depends on the endpoint selection

DOD HBCU Collaborative Summer Undergraduate Research
Program: Prostate Cancer Research Training Curriculum

14

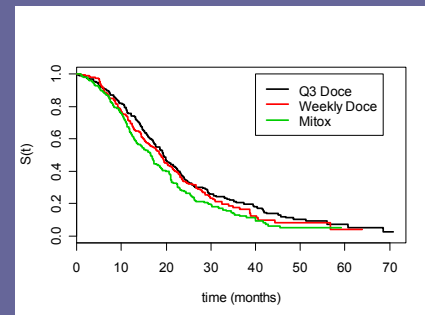
Estimation in TAX 327

- Outcome of interest is overall survival
- We can estimate
 - median survival: the time at which 50% of patients are still alive
 - 5 year survival: the proportion of patients that are still alive at 5 years
- These are called “point estimates”
- Other aims?
 - the mean change in quality of life from baseline to follow-up
 - the proportion of men with increased PSA at end of treatment

DOD HBCU Collaborative Summer Undergraduate Research
Program: Prostate Cancer Research Training Curriculum

15

Survival Curves of Treatment Groups



DOD HBCU Collaborative Summer Undergraduate Research
Program: Prostate Cancer Research Training Curriculum

16

Median survival

- Docetaxel every 3 wks: Median survival = **19.4 months**
- Docetaxel weekly: Median survival = **18.7 months**
- Mitoxantrone: Median survival = **16.6 months**
- Which looks to be the best?

DOD HBCU Collaborative Summer Undergraduate Research
Program: Prostate Cancer Research Training Curriculum

17

Another key part of estimation

- **Precision**: how certain are we of our point estimates?
- Variance or standard errors are important!
- We often use “Confidence intervals” to describe our certainty in our estimates
- A **95% confidence interval**: provides an interval that we are 95% certain contains the true parameter estimate
- 95% is most common, but we also see 90% and 99%.

DOD HBCU Collaborative Summer Undergraduate Research
Program: Prostate Cancer Research Training Curriculum

18

Confidence intervals for Median survival in TAX327

	n	median	95% CI
Doce Q3	241	19.4	(17.6, 21.6)
Doce wk	217	18.7	(16.3, 21.2)
Mitox	228	16.6	(14.3, 18.6)

How to interpret these?

Testing

- Critical for these types of comparative studies!
- The drug company (and everyone else) wants to know if its drug is better than the old drug
- We test hypotheses:
 - hypothesis 0: survival is the same in the three groups
 - hypothesis 1: survival is different in the three groups.
- Depending on the type of outcome, we use different tests
- hypothesis 0 is called the “null”
- hypothesis 1 is called the “alternative”

Outcome of test: p-value

- The most common measure of whether or not the treatments are different is the ‘p-value’
- The p-value is the probability of observing the difference we did (or larger) *if the null hypothesis is true.*
- If the p-value is small, it means that the observed data is unlikely if there is really no difference
- If the p-value is large, it means that the observed difference is too small to provide evidence of a “real” difference
- Standard threshold for “significant” p-value?

TAX327

- The ‘logrank test’ is a type of test we use for testing overall survival
- The p-value for testing that all groups are the same is 0.007
- The p-value testing that survival in the Doce Q3 arm is the same as the Doce every week arm is 0.37
- The p-value testing that survival in the Doce Q3 arm is the same as the Mitox arm is 0.009
- The p-value testing that survival in the Doce every week arm is the same as the Mitox arm is 0.10

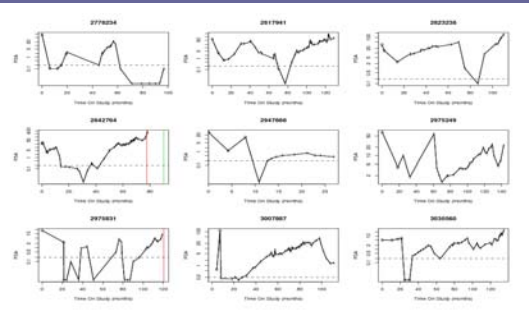
Additional biostatistical issues in prostate cancer research

- Measure of ‘response’
- Measuring time to progression or time to death

Prostate Specific Antigen

- **Prostate specific antigen (PSA)** is a protein produced by the cells of the prostate gland.
- PSA is present in small quantities in the serum of normal men, and is often elevated in the presence of prostate cancer and in other prostate disorders.
- A blood test to measure PSA is considered the most effective test currently available for the early detection of prostate cancer, but this effectiveness has also been questioned.
- Rising levels of PSA over time are associated with both localized and metastatic prostate cancer.

Prostate Specific Antigen (PSA)



DOD HBCU Collaborative Summer Undergraduate Research
Program: Prostate Cancer Research Training Curriculum

25

Tricky issues with PSA

- Change in PSA from baseline to post-treatment
- Potential problems
 - There is variability due to things other than cancer
 - day to day fluctuations
 - assay sensitivity
 - other prostate disorders
 - When you sample may give you different answers
 - Some question whether or not PSA is a good "surrogate measure"

DOD HBCU Collaborative Summer Undergraduate Research
Program: Prostate Cancer Research Training Curriculum

26

Surrogate measure

- What is the gold-standard measure in cancer treatment?
- Multiple choice:
 - A. time from treatment until disease goes into remission
 - B. time from diagnosis until disease progresses
 - C. time from treatment until death
 - D. time from diagnosis until death
 - E. time from treatment until disease progresses
 - F. time from diagnosis until disease goes into remission

DOD HBCU Collaborative Summer Undergraduate Research
Program: Prostate Cancer Research Training Curriculum

27

Surrogate measures in cancer research

- We generally assume the following:
 - if we can shrink the tumor, we can extend life
 - if we can delay tumor progression, we can extend life
- Are these valid assumptions?
 - sometimes yes, sometimes no
- Tumor shrinkage ("clinical response")
 - tumor response is often considered a poor surrogate
- Time to progression
 - tumor progression is often valid surrogate
 - however, it is hard to measure

DOD HBCU Collaborative Summer Undergraduate Research
Program: Prostate Cancer Research Training Curriculum

28

RECIST criteria

- RECIST criteria offer a simplified, conservative, extraction of imaging data for wide application in clinical trials. They presume that linear measures are an adequate substitute for 2-D methods and registers four response categories:
 - CR (complete response) = disappearance of all target lesions
 - PR (partial response) = 30% decrease in the sum of the longest diameter of target lesions
 - PD (progressive disease) = 20% increase in the sum of the longest diameter of target lesions
 - SD (stable disease) = small changes that do not meet above criteria

<http://imaging.cancer.gov/clinicaltrials/imaging/>

DOD HBCU Collaborative Summer Undergraduate Research
Program: Prostate Cancer Research Training Curriculum

29

Potential Problems with RECIST

- Stable disease includes both improvements and worsening
- Tumors are 3-D. RECIST only allows for 1-D.
- Implicitly makes the assumption that all lesions are spherical
- Measures are hence fraught with measurement error.
- Tumors with minor differences (e.g., 32% decrease and 28% decrease) are categorized differently.

DOD HBCU Collaborative Summer Undergraduate Research
Program: Prostate Cancer Research Training Curriculum

30

Time to event outcomes

- In cancer research, we are usually interested in measuring time until an event occurs
- the event is *usually* bad so we are trying to prevent the event from occurring
- inevitably, at the end of the study, many patients will not have had the outcome.
- These events that are not observed is called 'censored'
- More specifically, "right censored"

DOD HBCU Collaborative Summer Undergraduate Research
Program: Prostate Cancer Research Training Curriculum

31

Simple example:



DOD HBCU Collaborative Summer Undergraduate Research
Program: Prostate Cancer Research Training Curriculum

32

Introduce "administrative" censoring



DOD HBCU Collaborative Summer Undergraduate Research
Program: Prostate Cancer Research Training Curriculum

33

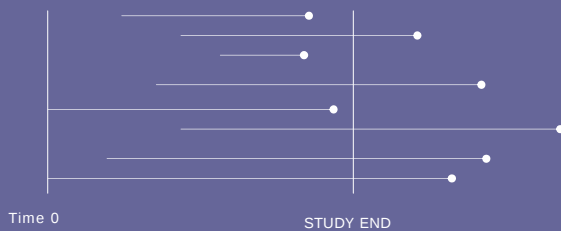
Introduce "administrative" censoring



DOD HBCU Collaborative Summer Undergraduate Research
Program: Prostate Cancer Research Training Curriculum

34

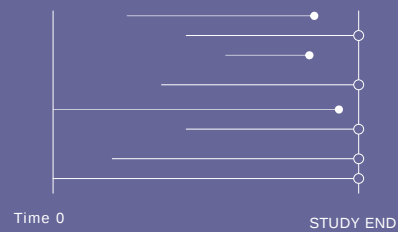
More realistic: clinical trial



DOD HBCU Collaborative Summer Undergraduate Research
Program: Prostate Cancer Research Training Curriculum

35

More realistic: clinical trial



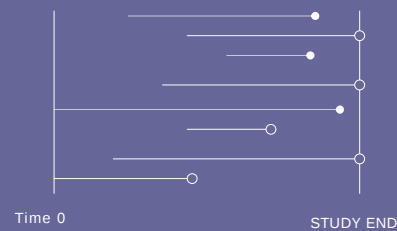
DOD HBCU Collaborative Summer Undergraduate Research
Program: Prostate Cancer Research Training Curriculum

36

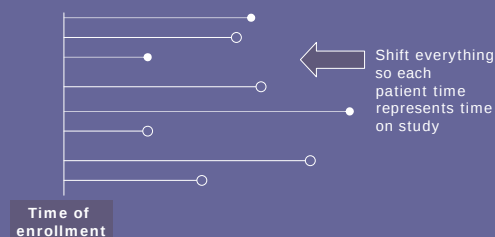
Additional issues

- Patient drop-out
- Loss to follow-up

Drop-out or LTFU



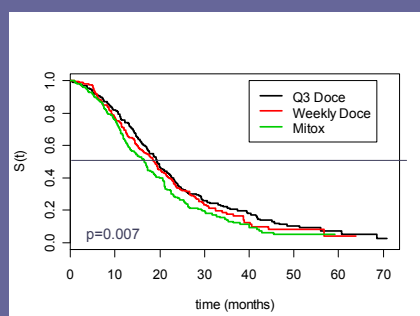
How do we “treat” the data?



Set of tools for time-to-event outcomes

- “Survival analysis”
- Kaplan-Meier curves: graphical representation
- Kaplan-Meier estimation: provides point estimates and confidence intervals
- Logrank test: tests for differences across groups

Kaplan-Meier curves



Summary

- Biostatisticians have a lot of tools for helping with prostate cancer research
- Critical areas of assistance:
 - study design
 - sample size estimation
 - data analysis
- Prostate cancer has some specific areas that make it challenging
 - measurement issues with standard outcomes
 - time to event outcomes require special methods

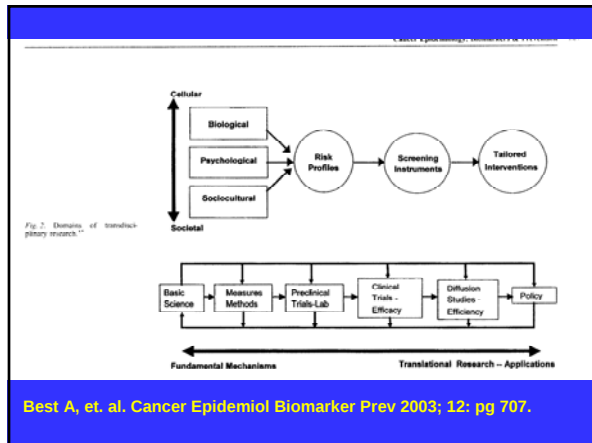
Epidemiology of Prostate Cancer

Summer Undergraduate Research Program
July 7, 2010
Anthony J. Alberg

Cancer Control:

- “Cancer control research is the conduct of basic and applied research in the behavioral, social and population sciences that, independently or in combination with biomedical approaches, reduces cancer risk.”

1997 NCI Report



Ultimate goal is to reduce burden of prostate cancer:

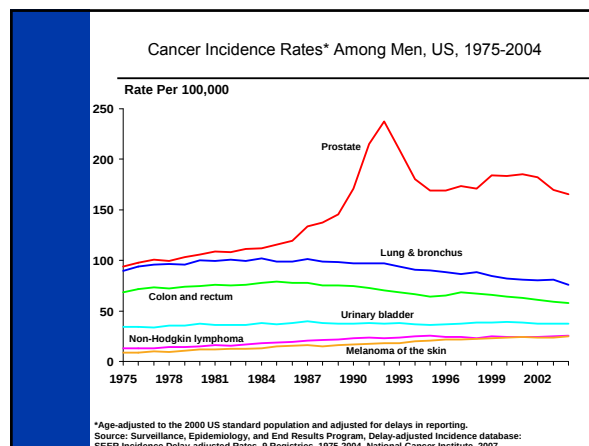
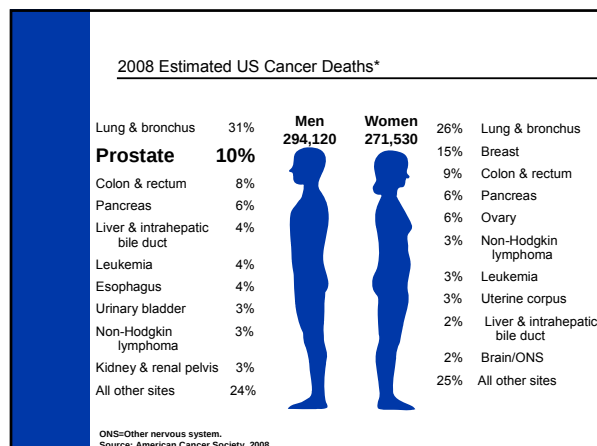
- Prevention
- Early detection
- Prolong Survival

To develop strategies to prevent prostate cancer, we need to understand its distribution in populations

2008 Estimated US Cancer Cases*

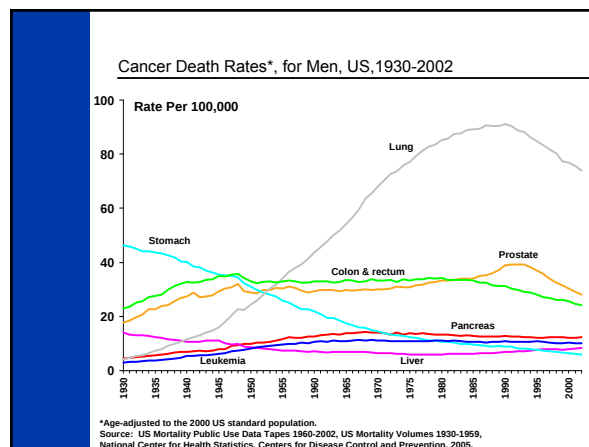
	Men 745,180	Women 692,000
Prostate	25%	
Lung & bronchus	15%	26% Breast
Colon & rectum	10%	14% Lung & bronchus
Urinary bladder	7%	10% Colon & rectum
Non-Hodgkin lymphoma	5%	6% Uterine corpus
Melanoma of skin	5%	4% Non-Hodgkin lymphoma
Kidney & renal pelvis	4%	4% Thyroid
Oral cavity	3%	4% Melanoma of skin
Leukemia	3%	3% Ovary
Pancreas	3%	3% Kidney & renal pelvis
All Other Sites	20%	3% Leukemia
		23% All Other Sites

*Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.
Source: American Cancer Society, 2008.



Age-adjusted prostate cancer incidence rate by racial/ethnic group, SEER 2002-2006

Group	Rate (per 100,000)
European American	153
African American	240
Hispanic	133
Asian	91
American Indian/Alaskan Native	76



Cancer Sites in Men for Which African American Death Rates* Exceed White Death Rates*, US, 2000-2004

Site	African American	White	Ratio of African American/White
All sites	321.8	234.7	1.4
Prostate	62.3	25.6	2.4
Larynx	5.0	2.2	2.3
Stomach	11.9	5.2	2.3
Myeloma	8.5	4.4	1.9
Oral cavity and pharynx	6.8	3.8	1.8
Small intestine	0.7	0.4	1.8
Liver and intrahepatic bile duct	10.0	6.5	1.5
Colon and rectum	32.7	22.9	1.4
Esophagus	10.2	7.7	1.3
Lung and bronchus	95.8	72.6	1.3
Pancreas	15.5	12.0	1.3

*Per 100,000, age-adjusted to the 2000 US standard population.
Source: Surveillance, Epidemiology, and End Results Program, 1975-2004, Division of Cancer Control and Population Sciences, National Cancer Institute, 2007.

Cancer Survival*(%) by Race, 1996-2003

Site	White	African American	Absolute Difference
All Sites	67	57	10
Breast (female)	90	78	12
Colon	66	55	11
Esophagus	18	11	7
Leukemia	51	40	11
Non-Hodgkin lymphoma	65	56	9
Oral cavity	62	41	21
Prostate	99	95	4
Rectum	66	58	8
Urinary bladder	81	65	16
Uterine cervix	74	66	8
Uterine corpus	86	61	25

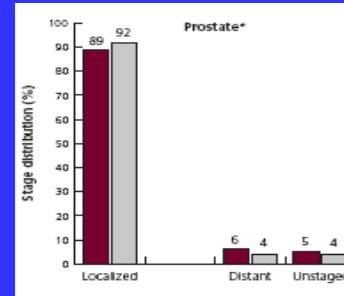
*5-year relative survival rates based on cancer patients diagnosed from 1996 to 2003 and followed through 2004.
Source: Surveillance, Epidemiology, and End Results Program, 1975-2004, Division of Cancer Control and Population Sciences, National Cancer Institute, 2007.

Trends in Five-year Relative Survival (%)* Rates, US, 1975-2003

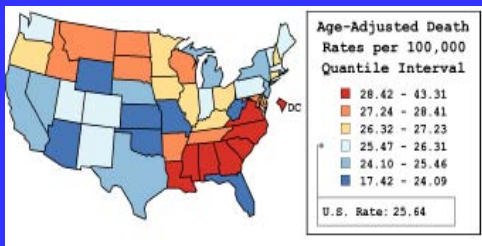
Site	1975-1977	1984-1986	1996-2003
All sites	50	54	66
Breast (female)	75	79	89
Colon	51	59	65
Leukemia	35	42	50
Lung and bronchus	13	13	16
Melanoma	82	87	92
Non-Hodgkin lymphoma	48	53	64
Ovary	37	40	45
Pancreas	2	3	5
Prostate	69	76	99
Rectum	49	57	66
Urinary bladder	74	78	81

*5-year relative survival rates based on follow up of patients through 2004.
Source: Surveillance, Epidemiology, and End Results Program, 1975-2004, Division of Cancer Control and Population Sciences, National Cancer Institute, 2007.

Stage distribution for AA (red) and EA (gray), US 1996-2004



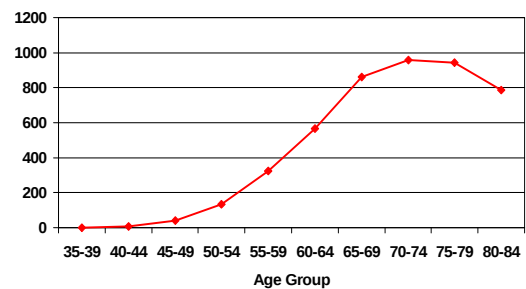
Geographic distribution of prostate cancer mortality rates by state, US 2002-2006

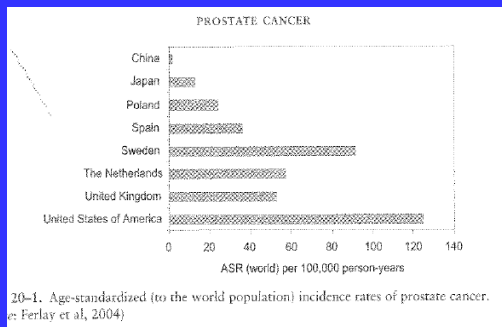


To develop strategies to prevent prostate cancer, we need to understand its causes

The single strongest individual risk factor for prostate cancer is older age.

Age-specific prostate cancer incidence rates (per 100,000), SEER 2002-2006





Source: Adami et al.

The results of migrant studies suggest that environmental risk factors are important to the etiology of prostate cancer, but the specific factors have proven difficult to identify.

A significant challenge to epidemiologic studies of prostate cancer is uncertainty about the “disease-free” controls or comparison group

Cigarette Smoking and Prostate Cancer

- Evidence of association with prostate cancer mortality, but not incidence
- Association stronger during 1st 10 years of follow-up
- Hypothesis: Smoking associated with more aggressive disease

Cigarette Smoking and Prostate Cancer RRs (95% CLs), Washington County, MD 1963-1973 (1st 10 yrs of follow-up)

Smoking Status	Incidence	Mortality
Former	1.5 (0.9, 2.4)	3.2 (1.3, 8.3)
Current >20 cigs/d	1.5 (0.8, 2.9)	3.5 (1.0, 12.4)

Source: Rohrmann S,....Platz EA. J Urology 2007

Summary of Evidence on Dietary Factors and Prostate Cancer

<u>Protects</u>	<u>Risk</u>
Selenium Vit. E Lycopene Vit. D Fish intake	Calcium/Dairy Fat

Source: Adami HO et al

Major inherited susceptibility

- Genetic testing for mutations that confer major inherited susceptibility cannot provide a "cure", but can provide clinically useful information.
- Examples:
 - enhanced surveillance for colorectal polyps (FAP) or breast cancer (BRCA1/BRCA2)
 - organ removal (e.g., prophylactic mastectomy for BRCA1/BRCA2).
 - For prostate cancer, currently none



Common genetic variants associated with small increases in risk

- Ongoing research is attempting to characterize how common genetic variation affects inter-individual susceptibility to prostate cancer (and prostate cancer risk factors)
- A promising lead: 8q24



What steps can we take for the primary prevention of cancer?



Can we take a pill to prevent cancer?



CHEMOPREVENTION

The use of natural (e.g., selenium, vitamin E) or synthetic (e.g., aspirin) to reduce the risk of developing cancer

Examples of chemoprevention: Prostate Cancer

- **SELECT Trial**
 - **Bad news:** no evidence that either selenium or vitamin E supplements protects against the development of prostate cancer
 - ~35,000 men followed for ave. 5.5 yrs

Age-adjusted prostate cancer incidence rate by racial/ethnic group, SEER 2002-2006

Group	RR (99% CI)
Placebo	1.0 (referent)
Vitamin E	1.13 (0.95-1.35)
Selenium	1.04 (0.87-1.24)
Both	1.05 (0.88-1.25)

Source: Lippman SM, et al JAMA 2009; 301: 39-

What steps can we take
for the secondary prevention
of cancer?



Cancer is a fearsome disease,
but it is much less fearsome if
detected early rather than late.



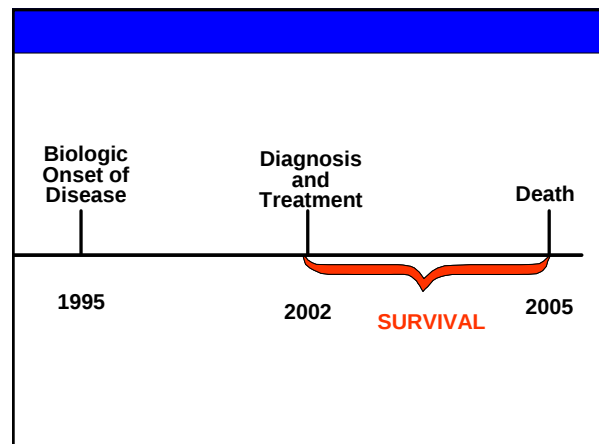
A strong determinant of a
cancer patient's survival is
stage of disease.

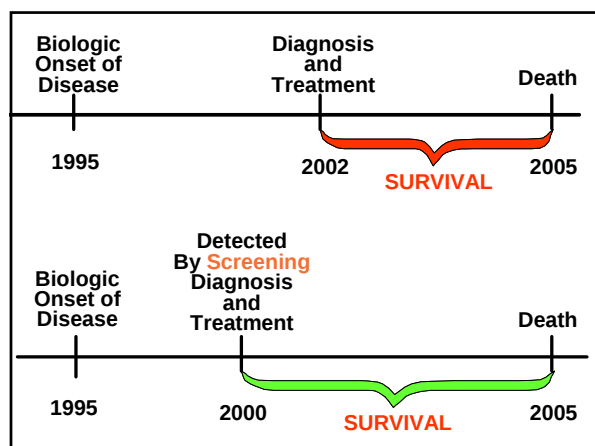
A strong determinant of a
cancer patient's survival is
stage of disease.

So, a screening test that can
shift the population
distribution of stage of
disease should be embraced,
right?

Cancer screening: all that
glitters is not gold

- How accurate is the screening test?
- Does the test achieve the intended benefit of reduced mortality? (Is there an effective available treatment that will reduce mortality when cancer is treated earlier?)
- Is the test acceptable to the public?





PSA Testing for Prostate Cancer: Results of RCTs

- 2 randomized controlled trials published earlier this year in New England Journal of Medicine
- Neither study showed significant benefit in reducing prostate cancer mortality
- Strong evidence that PSA testing is not efficacious

PSA Testing for Prostate Cancer: PLCO Trial

- ~77,000 men randomized to PSA testing vs "usual care"
- Intervention: annual PSA testing for 6 years and DRE for 4 years
- 7 years of follow-up
- Mortality rate (intervention vs control): 1.13 (0.75-1.70)

Source: Andriole GL et al NEJM 2009; 360: 1310--

Screening Guidelines for the Early Detection of Prostate Cancer, American Cancer Society

For men at average risk and high risk, information should be provided about what is known and what is uncertain about the benefits and limitations of early detection and treatment of prostate cancer so that they can make an informed decision about testing.

Applied Cancer Screening

- Given a screening test of proven efficacy, research will be needed to identify and overcome barriers to screening



Epidemiology of Prostate Cancer

Summer Program
July 22, 2009
Anthony J. Alberg

Genetic Epidemiology of Prostate Cancer

Overview

1. Genetic Epidemiology
2. The Human Genome
3. Genetic Variation
4. Types of Genetic Studies: Design and Analysis
5. Genetic Susceptibility to Prostate Cancer
6. Resources

Basics of Genetic Epidemiology

What is genetic epidemiology?

- The study of why some families are more susceptible to developing certain diseases
- Also why some populations are more susceptible to certain diseases
- Example: individuals of eastern european jewish descent have higher rates of breast and ovarian cancer

Implications

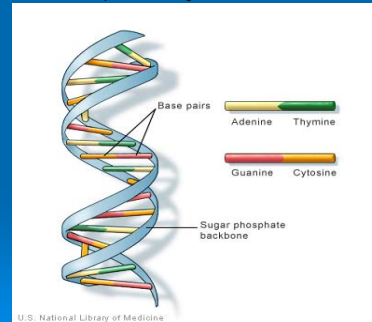
- Study of families (or populations) to discover inherited genes that increase risk of disease
- Discovery of these genes helps biologists understand mechanisms of disease and may lead to the development of therapies for prevention or treatment

How do we study genetic risk?

- Understand the basics of the human genome
- Understand what parts of the human genome are more common in families or populations at higher risk of disease
- Start with DNA

Describing the Human Genome

DNA (Deoxyribonucleic Acid)



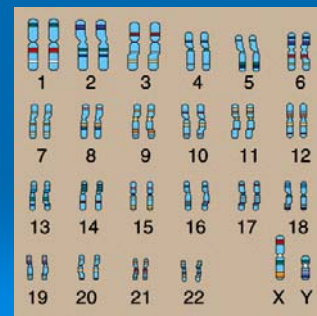
Double
Stranded.
Linked at
base pairs
(A-T; C-G)

DNA (cont.)

- Certain regions of DNA, called genes, code for amino acids and thus proteins
- A lot of DNA between genes (intergenic regions)
- Complete DNA sequence known as the human genome: approximately 25,000 protein-coding genes
- 3 billion base pairs across 23 chromosomes

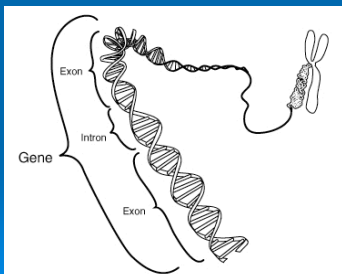
Human Chromosomes

23 chromosome *pairs* : 22 autosomal and X/Y or X/X



Genes

Consist of coding and non-coding regions
Non-coding regions are removed from mRNA
Approximately 2% of genome consists of protein coding sequences



Studying DNA

- Most of the human genome is the same across individuals but some variations occur
- Goal is to discover regions of DNA that DIFFER between individuals with and without disease
- Isolate genetic risk factors
- Understand more about biology of disease and possible treatments

Sources of Genetic Variation

Variation in the Human Genome

- 99.9% of genome of any two unrelated individuals is identical
- Genetic mutations result from changes in base pair sequence (causes include copying error, radiation, viruses, or chemical mutagens; germ-line mutations inherited)
- Sequence variations that result in altered protein function may have health consequences
- Common type of variation: single nucleotide polymorphism (SNP)

SNP

- Single Nucleotide Polymorphism
- Nucleotides are bases (A, T, G, C)
- Common SNP: variation in at least 1% of population
- Occur every 100 to 300 base pairs (at least 10 million SNPs in genome)
- At least two "alleles" (e.g. A or G) possible at given locus

SNP (cont)

- Many SNPs are in non-coding regions
- Non-coding SNPs could alter transcription (the process of creating RNA from DNA)
- Non-synonymous SNP – alters amino acid coding proteins
- Synonymous SNP – in coding region but does not alter protein structure

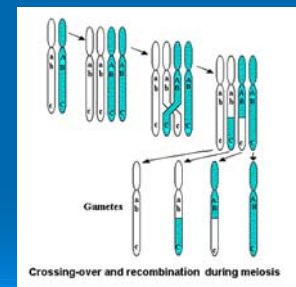
ALLELE

- Version of SNP (e.g. G or T)
- "Minor allele" is the less common version
- MAF – minor allele frequency – describes how common the SNP is in the population
- Refers to any type of genetic variation (not just SNPs)

Linkage Disequilibrium (LD)

Because of recombination, sequences of DNA that are closer together on a chromosome, are more likely to be inherited together.

Leads to strong association between two distinct loci (e.g. a & b but not c in Figure)



tag SNPs

- tag SNPs are SNPs that identify most of the variation in a given gene or region
- tag SNPs are in high LD with neighboring SNPs
- most genetic variation in a region can be genotyped w/o typing all SNPs

Types of Genetic Studies: Design and Analysis

Linkage Analysis

- Linkage mapping conducted in families in hopes of discovering regions conserved across multiple affected generations
- Genes for monogenic (caused by 1 gene) conditions have been located
- Not finely-mapped thus multiple genes may fall under a linkage "peak"

Association Studies

- Determine whether genetic markers are associated with traits in broader population
- Generally more finely-mapped than linkage studies
- Approaches include family-based association studies (trios/tetrads) and population-based association studies (case/control)

Genome Wide Association Studies

- High density SNP arrays now available (up to 1 million SNPs can be genotyped giving genome-wide coverage)
- Generally 1,000s of subjects genotyped (most cost effective to collect cases and controls)
- Need statistical power necessary to detect associations after correcting for multiple comparisons (testing thousands of SNPs)

Candidate Genes & SNPs

- Custom arrays designed to interrogate candidate genes (up to 1,500 SNPs)
- Candidate genes may be in known disease pathways or discovered in genome-wide studies or linkage analysis
- Fine-mapping may be explored with candidate gene interrogation
- Resequencing of candidates (all base pairs)

Family-based Association Studies

- Families genotyped (parents and affected offspring plus possibly unaffected siblings)
- Trio/tetrad designs
- Twin and sib-pair designs

Phenotypes : Binary Traits

- Testing for differences in MAF (minor allele frequencies) between cases and controls
- Testing for differences in transmission of alleles from parents to affected offspring
- Testing for genotype differences between sib-pairs

Phenotypes: Quantitative Traits

- Testing for different means across genotype groups (AA/AT/TT) using linear regression
- Testing for correlation between inherited alleles and phenotypes in families
- Heritability: estimate of phenotypic variance attributable to genetic effects

Genetic Susceptibility to Prostate Cancer: what have we learned?

Family Studies

- Relative risk of prostate cancer in individuals who have first-degree relatives (brothers, fathers) with prostate cancer has been reported to be greater than 2
- Greater if family members diagnosed at a young age or multiple affected family members
- Twin studies show that monozygotic (identical) twins have higher relative risk than dizygotic (same genetic similarity as siblings) twins
- Evidence that the breast cancer susceptibility gene BRCA2 increases risk of prostate cancer as well (only explains 10% of familial prostate cancer though!)

Family Studies: Linkage

- Linkage studies in families with multiple affected individuals have not found reproducible genetic loci
- Suggests that there isn't a prostate cancer gene (or even a few)
- Genetic predisposition comes from many common risk variants (true of many common diseases)
- Common disease-common variant theory

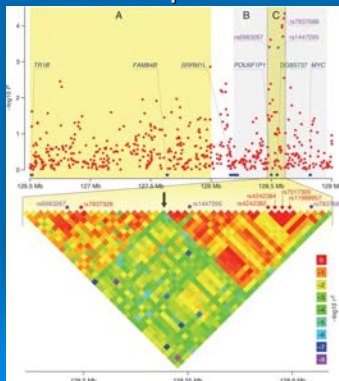
Genome-wide Association Studies

- Testing common SNPs without any prior assumptions
- Common SNPs on chromosomes 8 (8q24) and 17 (17q12 and 17q24) have been replicated as being risk variants in multiple populations (caucasian american, african american, icelandic)
- The SNP on 8q24 is relatively uncommon in individuals of european descent (MAF of 4%) and common in individuals of african descent (MAF of 42%)
- Higher incidence in AA may be partially attributed to this loci

8q24

- Genetic variants in this region also associated with earlier age at diagnosis
- Biologic implications?
- What gene is in this region – doesn't map to a known gene!
- Doesn't mean that the genetic region isn't important BUT interpretation is MUCH harder
- Could be a genomic instability mechanism (prone to deletions and duplications)

8q24



Other regions implicated

- Region on chromosome 11 (11q13) – no known gene
- *TCF2* gene on chromosome 17 (17q2) which is also implicated in type II diabetes (higher risk of diabetes is associated with lower risk of prostate cancer)
- *KLK2* and *KLK3* genes on chromosome 19 (19q13) which are involved in PSA production
- More work needs to be done!

Resources

HAPMAP

- International HapMap Project: goal to develop a map of the human genome
- Identified over 3 million SNPs in the most recent "build" released in 2009
- Genotyping 270 individuals from four populations (30 US families of European descent, 30 Yoruban families from Nigeria, 45 unrelated subjects from Beijing and 45 from Tokyo)
- Other populations have been added: Indians, Kenyans, Mexican Americans, Italians
- LD patterns and allele frequencies described in populations useful for determining tagSNPs

To Learn More:

- HapMap: www.hapmap.org
- National Center for Biotechnology Information database (dbSNP):
www.ncbi.nlm.nih.gov/projects/SNP
- UCSC genome browser: www.genome.ucsc.edu
- Burton PR, Tobin MD, and Hopper JL (2005). "Key concepts in genetic epidemiology." *Lancet* 366: 941-951.

To Learn More:

- Gudmundsson J et al. (2007). "Genome-wide association study identifies a second prostate cancer susceptibility variant at 8q24." *Nat Genet* 39: 631-637.
- Yeager M et al. (2007) "Genome-wide association study of prostate cancer identifies a second risk locus at 8q24" *Nat Genet* 39: 645-649.
- Freedman ML et al. (2006) "Admixture mapping identifies 8q24 as a prostate cancer risk locus in African-American men." *Proc Natl Acad Sci USA* 103: 14068-14073.
- Hooker S et al. (2010) "Replication of prostate cancer risk loci on 8q24, 11q13, 17q12, 19q33, and Xp11 in African Americans." *The Prostate* 70: 270-275.

Recruitment, Retention, Surgical and Medication Adherence Studies with African Americans: Lessons Learned

Marvella E. Ford, Ph.D.
Medical University of South Carolina
Associate Director, Cancer Disparities
Associate Professor, Department of Medicine



Topic Areas to be Discussed

Four topic areas will be discussed today:

- Recruitment intervention testing
- Retention intervention testing
- Cancer screening adherence assessment
- Medication adherence assessment

2

Presentation Outline

- Statement of the Problem
- Conceptual Framework
- Study 1: AAMEN Project
- Study 2: Case Management/ Patient Navigation Study
- Study 3: Comorbidities Study
- Studies 4-5: Surgical Adherence Studies
- Study 6: Medication Utilization Study
- Overall Conclusions

3

Statement of the Problem

- Despite their higher incidence and mortality of cancer compared to their Caucasian counterparts, African American men are not well-represented in cancer screening trials
- There is a lack of randomized trials testing the effectiveness of different recruitment and retention strategies in this population

4

Conceptual Framework



Swanson GM, Ward AJ. Recruiting minorities into clinical trials: toward a participant-friendly system. *JNCI* 1995

5

The AAMEN Project

Recruiting African American Men to the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial

Study 1

6

Peer-Reviewed Publications Related to the AAMEN Project

- Pinsky PF, Ford M, Gamito E, Higgins D, Jenkins V, Lamerato L, Tenorio S, Marcus PM, Gohagan JK. Enrollment of racial and ethnic minorities in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. *Journal of the National Medical Association* 2008;100:291-298.
- Ford ME, Havstad SL, Davis SD. A randomized trial of recruitment methods for older African American men in the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial. *Clinical Trials* 2004;1:343-351. Associated editorial: *Clinical Trials* 2004;1:341-342.
- Ford ME, Havstad SL, Tilley BC. Recruiting older African American men to a cancer screening trial (The AAMEN Project). *The Gerontologist* 2003;43:27-35.
- Stallings FL, Ford ME, Simpson NK, Fouad M, Trauth JM, Jernigan JC. Black participation in the PLCO Cancer Screening Trial. *Controlled Clinical Trials* 2000;21:379S-389S.

7

AAMEN Project Overview

AAMEN Project Design

- A randomized trial
- Designed to test the efficacy of three increasingly intensive recruitment strategies
- Conducted in the context of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial

8

Overview of the PLCO Cancer Screening Trial

Primary Objective:

- To determine whether screening for the 4 cancers decreases mortality due to these cancers in adult study participants aged 55-74 years
- 22-year multi-site randomized cancer screening trial
- Funded by the National Cancer Institute

9

PLCO Cancer Screening Trial Procedures

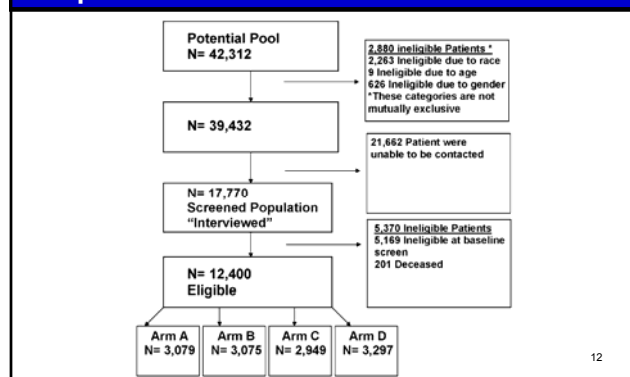
Test	Prostate Cancer	Lung Cancer "Ever-smokers"	Lung Cancer "Never-smokers"	Colorectal Cancer
Baseline	PSA DRE	Chest x-ray	Chest x-ray	Flexible sigmoidoscopy
Year 1	PSA DRE	Chest x-ray	Chest x-ray	
Year 2	PSA DRE	Chest x-ray	Chest x-ray	
Year 3	PSA DRE	Chest x-ray		
Year 4	PSA			
Year 5	PSA			Flexible sigmoidoscopy

AAMEN Project Study Sample

- African American males aged 55-74 years
 - Community residents of southeastern Michigan (and northern Ohio)

11

Sample Identification and Selection



12

Summary of AAMEN Project Study Processes (H_a = C>B>A>D)

Processes	Arm A	Arm B	Arm C	Arm D
Intro. Mailing	Enhanced	Enhanced	Enhanced	Standard
Telephone Interview Eligibility Screener	African American Interviewer	African American Interviewer	African American Interviewer	African American or Caucasian Interviewer
Mailing	Confirmation			
Telephone Reminder Call	Church Session			
Baseline Questionnaire (BQ) Information and Consent Form (CF)	Mailed BQ Packet	Telephone Interview for BQ & Mailed CF	Project Session Held at Church	Mailed BQ Packet
Telephone Reminder Call	Completed BQ Packet	Signed CF		Completed BQ Packet

AAMEN Study Recruitment using the Conceptual Framework

Addressing Economic Barriers

- Provided transportation to project meetings

Addressing an Individual Barrier: Denial

- Worked with key community leaders (Arm A-C)
- Emphasized the importance of the participants to their families and communities (Arm A-C)

Addressing Barriers Inherent in Study Design

- Gathered baseline information via a telephone interview (Arm B)
- Gathered baseline information at a community-based project session (Arm C)
- Participants never see each other face to face

Addressing Sociocultural Barriers: Fear and Mistrust

- Tailored recruitment strategies to the characteristics of the individuals to be enrolled
- Used population-based strategies (Arms A-D)
- Formed partnerships with community organizations (Arm C)
- Included research team members with racial backgrounds similar to those potential participants (Arms A-D)
- Conducted follow-up telephone calls (Arms A-D)

14

Mean Age, Age Range, and Income Level of African American Men in the AAMEN Project, by Contact Status

	Contacted n (column %)	Not Contacted n (column %)	P-value
Mean age (SD)	62.0 (5.7)	65.0 (6.0)	P<0.001
Age range (in years)			P<0.001
55-59	3,954 (25.3)	8,230 (44.0)	
60-64	3,694 (23.6)	5,307 (28.3)	
65-69	4,033 (25.8)	2,807 (15.0)	
70-74	3,962 (25.3)	2,380 (12.7)	
Income level			P<0.001
Low	6,222 (35.0)	8,765 (40.5)	
Mod-to-High	11,548 (65.0)	12,897 (59.5)	

Randomization of AAMEN Project participants to the PLCO Cancer Screening Trial by Study Arm

	Arm A n= 3,079	Arm B n= 3,075	Arm C n= 2,949	Arm D n= 3,297
Yield (n/number contacted and found eligible)	2.5%	2.8%	3.9%	2.9%

* Arm C had a significantly higher yield than arm D (control arm), P=0.022

16

Summary

- Arm C, with the highest amount of face-to-face contact, had the highest recruitment yield
- The screenings offered through the PLCO Cancer Screening Trial may have been an incentive for study participation for men from lower SES groups

17

Enhancing Cancer Screening Trial Retention among Older African American Men:

Randomized Trial Design Using a Case Management/Patient Navigation Approach

Study 2

18

Peer-Reviewed Publications Related to the Case Management Study

- Ford ME, Havstad SL, Vernon SW, Davis SD, Kroll D, Lamerato L, Swanson GM. Enhancing adherence among older African American men enrolled in a longitudinal cancer screening trial. *The Gerontologist* 2006;46:545-550.
- Ford ME, Randolph V, Hopkins-Johnson L, Eason SL, Havstad S, Jankowski M, Swanson GM, Vernon S. Design of a case management approach to enhance cancer screening trial retention among older African American men. *Journal of Aging and Health* 2004; Nov;16:39S-57S.

19

Rationale for the Case Management Approach

Our previous recruitment study showed that participants reported having a variety of human service needs that may have hindered their study participation

20

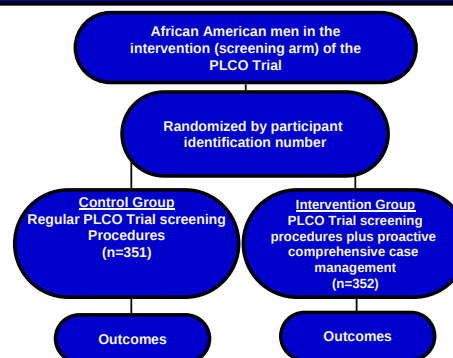
Study Methods

Sample

- Enrollees in the intervention arm of the PLCO Trial at the Henry Ford Health System site in Detroit, MI
- 703 African American men aged 55+ years living in the Detroit metropolitan area and in northern Ohio
- The participants were then randomly assigned to the case management intervention group (n=352) or to the control group (n=351)

21

Study Methods



22

The Case Management Intervention

- The case managers spoke with each participant in the intervention group at least once per month by telephone, and often much more frequently
- Tracking strategies were used to locate participants with disconnected telephone numbers:
<http://www.theultimates.com>, <http://www.switchboard.com>,
<http://www.whowhere.com>

23

Analytic Approach

- Logistic regression was used to test for an interaction between income and randomization group for each of the four types of screening tests (PSA, chest x-ray, DRE, and FSG)
- All overall comparisons were determined to be significant at the $p < 0.05$ level
- All within-income level comparisons were considered to be significant at the $p < 0.025$ level

24

Demographic Characteristics of the Study Sample

INTERVENTION (n=352)

Age: 63.1 (5.5%)
 Education: Some college or > (47%)
 Income: Moderate to high (68.5%)
 Marital Status: Married (67.8%)
 Work Status: Retired (59.7%)

CONTROL (n=351)

Age: 63.3 (5.4%)
 Education: Some college or > (41%)
 Income: Moderate to high (70.0%)
 Marital Status: Married (67.3%)
 Work Status: Retired (51.6%)

25

Post-Intervention Adherence Outcomes by Income Group

Type of Screening Test	Adhere (Yes/No)	Low Income			Moderate-to-High Income		
		Intervention (n=106) n (%)	Control (n=101) n (%)	p-value	Intervention (n=231) n (%)	Control (n=236) n (%)	p-value
PSA	Yes	78 (74.3)	53 (53.0)	0.001	155 (68.0)	158 (68.1)	0.98
	No	27 (25.7)	47 (47.0)		73 (32.0)	74 (31.9)	
DRE	Yes	53 (66.2)	35 (46.1)	0.011	95 (63.3)	109 (66.5)	0.56
	No	27 (33.8)	41 (53.9)		55 (36.7)	55 (33.5)	
Chest	Yes	56 (70.9)	39 (51.3)	0.012	97 (64.2)	113 (69.3)	0.34
	No	23 (29.1)	37 (48.9)		54 (35.8)	50 (30.7)	
FSG	Yes	31 (68.0)	20 (51.3)	0.10	50 (53.8)	60 (62.5)	0.22
	No	14 (31.1)	19 (48.7)		43 (46.2)	36 (37.5)	

Summary

- The case management intervention was most effective in retaining African American men with low income levels
- Greater attrition is typically seen in study participants with lower income levels

27

Summary (cont.)

- Men with lower income requested more services than other men (p=0.02)
- Elements of successful case management interventions require a sufficient planning phase to
 - Select and hire case managers
 - Identify and contact local service agencies
 - Develop an information and referral file

28

The Comorbidities Study

Effects of Baseline Chronic Conditions on Adherence in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO Trial)

Study 3

29

Peer-Reviewed Publication Related to the Comorbidities Study

Ford ME, Havstad SL, Fields ME, Manigo M, McClary B, Lamerato M. Effects of baseline comorbidities on cancer screening trial adherence among older African American men. Cancer Epidemiology, Biomarkers & Prevention. 2008;17:1234-9.

30

Purpose of the Adherence Study

- To examine the effects of baseline health factors on screening adherence in a sample of older African American men enrolled in the PLCO Trial (aged 55+ years)

31

Adherence Study Methods

- A longitudinal design was used
- 703 African American men aged 55 years and older in the previously described case management, patient navigation study
 - 352 men were assigned to a case management intervention group
 - 351 men were assigned to the case management control group
 - A case manager called each intervention group participant at least once per month

32

Adherence to PSA Screen by Group

Group	Disease Status	N	Adhere to PSA Screen? n (%)	p-value
Control	Current smoker -Yes	83	51 (61.4%)	0.052
	-No	152	95 (62.5%)	
Intervention	Current smoker -Yes	84	47 (56.0%)	
	-No	169	122 (72.2%)	

33

Adherence to the DRE Screening Test by Group

Group	Disease status	N	Adhere to DRE Screen? n (%)	p-value
Control	Chronic bronchitis -Yes	11	7 (63.6%)	0.063
	-No	194	120 (61.9%)	
Intervention	Chronic bronchitis -Yes	14	4 (28.6%)	
	-No	190	124 (65.3%)	

34

Adherence to Chest X-Ray Screening Test by Group

Group	Disease status	N	Adhere to Chest Screen? n (%)	p-value
Control	Chronic bronchitis -Yes	11	7 (63.6%)	0.045
	-No	193	127 (65.8%)	
Intervention	Chronic bronchitis -Yes	14	4 (28.6%)	
	-No	190	190 (66.3%)	
Control	Current smoker -Yes	70	40 (57.1%)	0.094
	-No	104	67 (64.4%)	
Intervention	Current smoker -Yes	68	35 (51.5%)	
	-No	124	85 (68.6%)	

Adherence to FSG Screen by Group

Group	Disease status	N	Adhere to FSG Screen? n (%)	p-value
Control	Arthritis -Yes	42	17 (40.5%)	0.022
	-No	73	51 (69.9%)	
Intervention	Arthritis -Yes	45	28 (62.2%)	
	-No	74	45 (60.8%)	

36

Summary

- Focus on African American men
- Results show that, in general, once participants are recruited, those with baseline co-morbidities are no less likely than those without baseline co-morbidities to adhere to the trial screenings
- Smokers had lower rates of screening adherence than non-smokers

37

Studies 4-5: Underuse of Surgical Resection among Whites and African Americans in South Carolina

Studies 4-5

38

Study 4: Independent Predictors of Surgical Resection in Patients with Localized, Non-Small Cell Lung Cancer (Funded by an NIH/NIA Pilot Grant, PI: Esnaola, Mentor: Ford)

Variable	OR (95% CI)	p Value
Age 70-79	0.48 (0.28-0.82)	0.0078
Age > 80	0.18 (0.10-0.32)	<0.001
African American race	0.43 (0.34-0.55)	<0.001
Separated or divorced	0.71 (0.52-0.97)	0.029
Widowed	0.60 (0.48-0.76)	<0.001
Comorbidity	0.69 (0.62-0.78)	<0.001
Living in poverty	0.67 (0.51-0.88)	0.005
HMO	0.47 (0.26-0.85)	0.013
Medicare	0.53 (0.39-0.72)	<0.001
Medicaid	0.37 (0.22-0.64)	0.0003
Self-pay	0.41 (0.25-0.67)	0.0004

Esnaola NF, Gebregziabher M, Knott K, Finney C, Silvestri GA, Reed CE, Ford ME. Underuse of surgical resection for localized, non-small cell lung cancer among whites and African Americans³⁹ in South Carolina. *Ann Thorac Surg*. 2008

Study 5: Colon Cancer: Independent Effect of Black Race on Surgical Resection (Funded by an NIH/NIA Pilot Grant, PI: Esnaola, Mentor: Ford)

	OR (95% CI)
1. Model 1: Race	0.76 (0.62-0.94)
2. Model 1 + demographics	0.73 (0.58-0.92)
3. Model 2 + comorbidity	0.68 (0.53-0.88)
4. Model 3 + SES	0.68 (0.52-0.88)
5. Model 4 + tumor factors	0.67 (0.51-0.88)

Esnaola NF, Gebregziabher M, Finney C, Ford ME. Underuse of Surgical Resection in Black Patients With Nonmetastatic Colorectal Cancer: Location, Location, Location. *Ann Surg*. 2009 Aug 27. [Epub ahead of print]

40

Study 6: Racial/Ethnic Disparities in Medication Use among Veterans with Hypertension and Dementia: A National Cohort Study

Study 4

41

Peer-Reviewed Publications Related to the Medication Use Study

1. Poon I, Lal LS, Ford ME, Braun UK. Racial/ethnic disparities in medication use among veterans with hypertension and dementia. *Ann Pharmacother*. 2009;43:185-93.
2. Poon I, Lal LS, Ford ME, Braun UK. Racial/ethnic differences in blood pressure control and medication utilization in a cohort of older veterans with dementia. *American Journal of Therapeutics* 2010;17:34-41.

42

Study Design and Sample

- Data were obtained from two national databases of the Veterans Health Administration (2000-2005)
- A total of 56,561 patients (70.5% Caucasian, 15.6% African American, and 6.6% Hispanic) aged 65 years and older had diagnoses of hypertension and dementia

43

Definition of Medication Adherence

- Adherence = a medication possession ratio (MPR) of 0.8 or greater
- The adherence variable was dichotomous, defined as either adherent or nonadherent

44

Analytic Approach

- Data were analyzed using SAS software
- Sociodemographic data were generated using descriptive statistics
- The independent sample t-test was used to make comparisons for the MPR
- All tests were 2-sided and a p value of < 0.05 was considered to be statistically significant

45

Analytic Approach (continued)

- Multivariate logistic regression analyses were adjusted for age, gender, marital status, and geographic location was used to assess the association between adherence and racial/ethnic group

46

Results

- The mean age was 78.9 years $\pm$ 6 years
- 97.0% of participants were male

47

Table 1. Multivariate Analysis for MPR and Race/Ethnicity^{ab}

Drug Class	African American vs White		Hispanic vs White	
	OR	95% CI	OR	95% CI
ACE inhibitors	0.74	0.66 to 0.84 ^c	0.82	0.67 to 1.00
ARBs	0.48	0.27 to 0.85 ^c	0.90	0.21 to 3.80
β -Blockers	0.72	0.62 to 0.83 ^c	0.86	0.67 to 1.09
Dihydropyridine calcium-channel blockers ^d	0.65	0.56 to 0.76 ^c	0.69	0.53 to 0.89 ^c
Nondihydropyridine calcium-channel blockers ^d	0.80	0.54 to 0.91 ^c	0.77	0.45 to 1.31
Loop diuretics	0.94	0.78 to 1.11	1.00	0.74 to 1.38
Potassium-sparing diuretics	0.75	0.44 to 1.29	1.20	0.42 to 3.50
Thiazide diuretics	0.84	0.71 to 0.99 ^c	0.86	0.64 to 1.15
α -Blockers	0.68	0.56 to 0.77 ^c	0.99	0.76 to 1.30
α -Agonists	0.48	0.35 to 0.66 ^c	0.73	0.35 to 1.53
Acetylcholinesterase inhibitors	0.72	0.62 to 0.83 ^c	0.77	0.61 to 0.96 ^c
Memantine	0.59	0.41 to 0.86 ^c	0.63	0.33 to 1.17
Vasodilators	0.46	0.28 to 0.72 ^c	1.17	0.42 to 3.23

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; MPR = medication possession ratio.

^aAdjusted for age, sex, marital status, and geographic location.

^bMPR is adherent if $\geq$ 0.8.

^cStatistically significant; $p < 0.05$.

^dNicardipine, isradipine, nisoldipine, amlodipine, nifedipine, felodipine.

^eDiltiazem, verapamil.

Summary

- African American patients with dementia received less acetyl cholinesterase inhibitors and the NMDA antagonist memantine compared with Caucasians
- Hispanics were less likely to be adherent to dihydropyridine calcium-channel blockers and acetyl cholinesterase inhibitors compared to Caucasians

49

Overall Conclusions of All Six Studies

- Caveat - Tremendous diversity among African Americans
- Wide range of socioeconomic status (2/3 of African Americans are not poor)
- Recognize gender and age/cohort differences

50

Overall Conclusions (continued)

- Older African American men will participate in cancer clinical trials with intensive recruitment methods employed
- A case management/patient navigation intervention can be successful in retaining men once recruited
- African American men with baseline comorbidities will adhere to trial methods

51

Overall Conclusions (continued)

- Targeted recruitment strategies for African American men may help to reach this population
- The wives of the men in the AAMEN Project play a significant gatekeeper role
- A high level of commitment to the inclusion of African American men in clinical trials is needed:
 - Making study sites more accessible
 - Funding and supporting African American investigators conducting these studies

52

Overall Conclusions (continued)

- The case management intervention was most effective among men with lower incomes
- Men with lower income requested more services than other men ($p=0.02$)
- Elements of successful case management interventions require a sufficient planning phase to
 - Select and hire case managers
 - Identify and contact local service agencies
 - Develop an information and referral file

53

Overall Conclusions (continued)

- African American men with baseline comorbidities are very good candidates for participation in longitudinal cancer screening trials
- Smoking status is a major barrier to adherence

54

Overall Conclusions (continued)

- African Americans underuse surgical resection
- African Americans and Hispanics with hypertension and dementia are less adherent than Caucasians to medication use for these diseases
- A case management/patient navigation intervention could be tested in this population as a means of increasing medication adherence rates

55

Acknowledgements

This research was supported by:

- CDC NCI Contract No. N01-CN-25512
- NIH/NCMHD EXPORT Grant No. P60 MD000267
- NIH/NIA/NINR Resource Center for Minority Aging Research (RCMAR) Grant No. 1 P30 AG 21677
- DoD Grant No. DAMD17-99-1-9005
- NIH/NCI 1 P30 CA138313-01 (Cancer Center Support Grant)

56

MUSC - 6 Colleges

- *Graduate Studies*
- *Medicine*
- *Pharmacy*
- *Nursing*
- *Health Professions*
- *Dental Medicine*



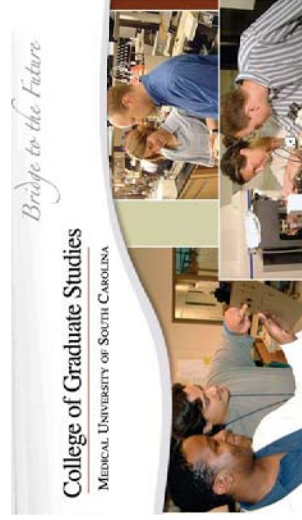
The Basics: What's a Ph.D.?

Ph.D.: Doctor of Philosophy degree

- Highest academic degree earned
- Terminal degree
- ~1% of the population is awarded
- Requires:
 - Extensive study
 - Intense intellectual effort
 - Scientific expertise



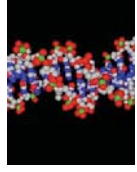
Drs. Brandon, Danshy, Freeman, Hagos, Handy, Owen, and Peprah
Emory University Fellowships in Research and Science Teaching (FIRST)



Dr. Cynthia Wright, Assistant Dean for Admissions
wrightcf@musc.edu

Benefits of a graduate school degree

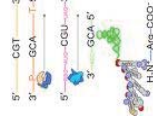
- Rewarding career opportunities
 - Make contributions to cutting edge science
- MS and Ph.D required for many positions
- Increased salaries in many biomedical careers
- Flexibility and independence
- Publishing in scientific journals



Who Should Do This?

People who:

- Have curiosity
- Enjoy solving problems
- Like to work independently
- Want to help others
- Are flexible about their careers



McGee and Keller (2007) CBE-Life Sciences Education, 6:316-331.

What can I do with my degree?



Academic Research

Teaching

Industry Research

Patent Law

Consulting

Entrepreneur

Medical Writing

Public Policy



Application Process

•Completed Application (including personal statement and CV)

•Transcripts from all colleges/universities attended

•Letters of recommendation - research mentors

•GRE general test - **PREPARE! PREPARE! PREPARE!**

•An interview (should) be required - know your research project - goals, aims, outcomes, future directions

- be coherent, organized, and succinct
- use an active, straight-forward voice
- be specific- get to the point!
- proof, revise, and then proof
- be honest- demonstrate confidence
- don't write a biography or catalog achievements
- don't use clichés, elaborate constructs, etc
- don't quote dead people
- don't lecture!
- don't start out with: I've always wanted to be....
- don't use vague qualifiers: challenging, rewarding, etc
- check your grammar and spelling! NO MISTAKES!!!

Choosing your graduate school

•Make sure that the graduate program fits your interests and goals

•Talk to faculty at your undergraduate institution

•Participate in Summer Undergraduate Research Programs

•Visit the institution

•Discover where graduates have gone

Writing an Effective Personal Statement

What are you trying to tell the reader?

1. The reason why you are applying
2. Your short- and long-term career goals
3. Your academic background
4. Past experiences- research and others
5. How (3) and (4) support (2), which then collectively justify (1).

What is the proper length?



One page is good- 1/3rd to 1/4th of a page is not

Tips on Preparing a Curriculum Vitae (CV)

“Course of Life” is the Latin translation of Curriculum Vitae.
What goes into a CV ?

Contact information

Who are you? Where are you from? Here, include your name, address, phone, fax, and e-mail for home and office, if applicable.

Education

Indicate your major, type of degree, and the date each degree was awarded for each postsecondary school attended

Teaching Experience List any courses that you assisted with as a TA, co-taught, or taught.

Conference Presentations

Similar to the section on publications, separate this category into sections for posters and papers. Use the appropriate documentation style for your discipline.

Professional Activities

List service activities, committee memberships, administrative work, lectures you've been invited to deliver, professional workshops you've delivered or attended, editorial activities, and any other professional activities in which you've engaged.

Professional Affiliations

List any professional societies with which you're affiliated, Honor or Scientific Societies, Student affiliate

Research Interests

Briefly summarize your research interests with four to six key descriptors. This is best added during graduate school than before.

Research Experience (Very important!)

List assistantships, summer undergraduate programs, and other research experience. Include the institution, nature of the position, duties, dates, and supervisor.

Grants Awarded

Include title of agency, projects for which funds were awarded, and dollar amounts.

Publications

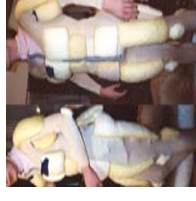
Put the full reference

References

Get permission ahead of time. Make sure they will speak highly of you.

Padding

Don't list lots of projects underway
Don't have more form than substance



No Padding!



Don't Exaggerate



OR



What Not to Put In

Don't overly personalize.



Pretty Cool People Club
Doughnut Appreciation Club



Fernando

Other considerations when preparing a CV:

QUALITIES OF AN EFFECTIVE CV

- * Easy to read
- * Clear and concise
- * Comprehensive but concise
- * Correct
- * **Be Honest**



CURRICULUM VITAE DISASTER AREAS

- * Poor appearance or format
- * Confusing or illogical organization
- * Incorrect grammar or word usage, misspellings, typographical errors
- * Poor photocopy
- * Lack of name, address or phone number
- * Unexplained time periods



- * Exaggerations or "padding"
- * Insufficient or contradictory information



Degrees Offered

- MS
- PhD
- MD/PhD
- PharmD/PhD
- DMD/PhD



MD/PhD Pathway:

- First 2 years of medical school (lab rotations in the summers)
- Step 1 USMLE
- 3-4 years research
- Final 2 years of medical school



PhD Application Process

- Completed Online Application (including personal statement and CV)
- Transcripts from all colleges/universities attended (3.0 GPA or greater) (3.4)
- Letters of recommendation (3)
- GRE general test (guideline is 1100 V+Q) (1220)
- Interview
- TOEFL test if international

Research experience is critical

MD/PhD Application Process

- Apply through AMCAS
- Apply online to MUSC MSTP program
- MCAT scores (32)
- GPA (3.5)
- Letters of recommendation
- Interview

Research experience is critical

PhD Pathway:

- First year core (interdisciplinary) curriculum
- Choose a program and a mentor/laboratory
- Advanced course work (12 hours)
- Written and oral qualifying exams
- Dissertation research
- Defend your dissertation



Graduate!

~5 years

Financial considerations

Stipend \$23,000-25,000/year

Paid health insurance

Dean's scholarship for tuition

APPENDIX D
Student Fellows' Research Papers

Jonathan L. Brown
Junior Biology Major, Claflin University
Mentor: Dr. Danyelle Townsend
MUSC Hollings Cancer Center

NOV-002 Induces S-Glutathionylation of Serpin A1 and A3 in Human Plasma

Abstract

Serine protease inhibitors (serpins) make up about 2% of the total protein in human serum. Serpins have been found to undergo post-translational modification, S-glutathionylation, in patients treated with redox chemotherapeutics. S-glutathionylation is the specific posttranslational modification of protein cysteine residues by the addition of glutathione. S-glutathionylation alters the functionality of enzymes, receptors, structural proteins, transcription factors, and transport proteins. The drug, NOV-002, is the redox chemotherapeutics utilized in this experiment to cause serpin A1 and A3 to glutathionylate in treated serum. After receiving the redox chemotherapeutics, glutathionylated Serpin A1 and A3 may affect myeloproliferative events. Using protein electrophoresis and Western blot analysis, glutathionylation of serpin A1 and A3 proteins was measured before and after the addition of the drug NOV-002 to serum samples of cancer patients. The results will evaluate the effects of the redox chemotherapeutics on the S-glutathionylation of serpins.

Introduction

The objective of this experiment is to identify the S-glutathionylation patterns of serpins in plasma from cancer patients via Western blot analysis. There is evidence that the Serpin protein family influences myeloproliferation and hematopoietic progenitor cell mobilization. The goal is to determine S-glutathionylated serpin patterns in relation to a cancer patient's myeloproliferative status. Hence after chemotherapy, the myeloproliferative status is low and in the future, this information will help to increase this condition. Evidence shows that the down-regulation of serpins A1 and A3 in bone marrow occurs during progenitor cell mobilization. These two serpin groups are responsible for inhibiting serine proteases in addition to lesser roles as hormone transporters, molecular chaperones, or even tumor suppressors. Glutathionylation of serpins may inhibit their activity, which may affect their role in key signaling pathways. Serpin A1 and Serpin A3 are S-glutathionylated in redox chemotherapeutic treated serum.

Materials

The following materials were utilized in this experiment in order to carry out experimental procedures:

- Eight plasma samples (taken from cancer patients)
- NOV-002
- Reduced GSH
- KH_2PO_4 , Potassium Phosphate
- Deionized, Distilled H_2O
- Eppendorf tubes (1.5mL)
- IGG (Immunoglobulins)
- 4XSD
- TBST (Tris-Buffered Saline Tween-20)
- Anti-PSSG (protein glutathione)
- Anti-Mouse
- Anti – Albumin
- Anti-Rabbit

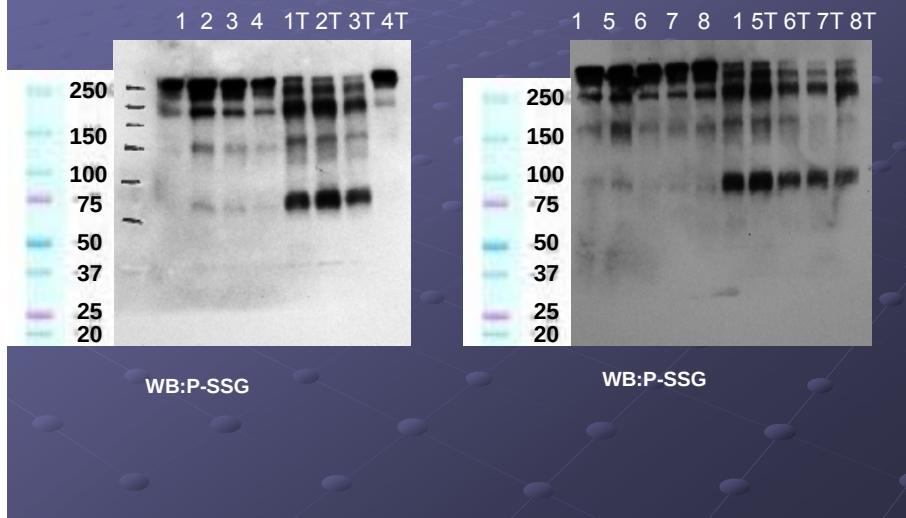
- Serpin A1 and Serpin A3

Method/Procedure

1. Calculate concentrations from stock solutions and use dilutions, calculate protein concentrations, and calculate all reagents
2. Thaw serum samples on ice- 1 hour to thaw – label samples 1-8 (representing the 8 plasma samples)
3. Preheat water bath at 37°C
4. Once samples are completely thawed, mix gently by inverting and calculate protein concentration using the Bradford Assay
5. Prepare 18 1.5mL eppendorf tubes (8 for treated samples, 8 for untreated samples, 1 extra treated, 1 extra untreated)
6. Add Potassium Phosphate, protein samples, add GSH(only in 9 samples), and then drug (only in 9 samples)-respectively
7. Put samples at 37C water bath- 1 hour
8. add 7uL of 4XSD immediately after removing from water bath
9. Centrifuge samples
10. Boil sample for 5 mins
11. Centrifuge samples again
12. Load two 7.5% gels (10 wells)
13. Run at 100V – 2hr
14. Transfer gel to membrane at 25-30V(over night)
15. Block in 5% Milk (2.5g milk/50mL TBST)
16. Probe in primary antibody (anti-PSSG) -two hours
17. Rinse 4X for 5 mins in TBST
18. Probe in secondary antibody (anti-mouse) -one hour
19. Image the membrane
20. Strip the membrane with stripping buffer
21. Repeat step 15
22. Probe in primary antibody (anti-albumin)- 2 hours
23. Repeat step 17
24. Probe in secondary antibody (anti-rabbit)- loading control -1 hour
25. Repeat Step 19
26. Repeat step 20 and 15 (respectively)
27. Probe in primary antibody (Serp A1)- 2 hours
28. Repeat step 17
29. Probe in secondary antibody (anti-goat)- 1hour
30. Repeat step 19
31. Repeat step 20 and 15 (respectively)
32. Probe in primary antibody (Serp A3) – 2 hours
33. Repeat step 17
34. Repeat step 29
35. Repeat step 19

Results

Western Blot Analysis of P-SSG



This western blot analysis was done on glutathionylation. The blot on the left indicates that the first four samples (1, 2, 3, and 4) were the untreated samples (no NOV-02). The last four samples indicates the samples that were treated (NOV-002 treated). The blot on the right shows the other plasma samples that were glutathionylated. The first five samples (1, 5, 6, 7, 8) are the untreated samples (no NOV-002) and the other five samples (1, 5T, 6T, 7T, 8T) are the treated samples. The glutathionylation patterns in both blots illustrates that glutathionylation is increased in the plasma samples that were treated with NOV-002. On the contrary, the plasma samples that were not treated with NOV-002 has less glutathionylation patterns compared to those that were treated with the drug.

Western Blot of Serpin A1



This western blot was done on the serpin group, Serpin A1. This blot illustrates that Serpin A1 are found in all of the eight plasma samples taken from cancer patients and are S-glutathionylated. The blot that is absent is Serpin A3. The glutathionylation performed on the Serpin A3 blot was too light to illustrate. Although the Serpin A3 blot is too light to show, Serpin A3 is present in all of the eight plasma samples as well.

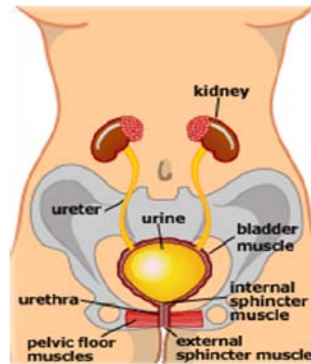
Conclusion

In conclusion, referring to the results that were gathered from this experiment, cancer patients have different Serpin A1 and A3 glutathionylation amounts after receiving the NOV-002 treatment. This proves that S-glutathionylation of serpins occur after receiving the chemotherapeutic or drug, NOV-002. This evidence may help with hematopoietic cell mobilization in bone marrow cells. This is significant to increase the low blood count of white blood counts in cancer patients after receiving chemotherapy. In essence, later studies can be conducted to better assist cancer patients and increasing their myeloproliferative status.

References

1. S-Glutathionylation : Indicator of Cell Stress and Regulator of the Unfolded Protein Response - Dr. Danyelle Townsend (2007)
2. Serine protease inhibitors serpinA1 and serpinA3 are down-regulated in bone marrow during hematopoietic progenitor mobilization - Ingrid G. Winkler (2005)
3. An Overview of the serpin superfamily - Ruby HP Law (2006)
4. Serpin-A1 and A3 as potential pharmacodynamic biomarkers for NOV-002, a redox modulating anticancer agent (2010)
5. Sulfiredoxin - Robert R. Bowers
6. www.wikipedia.com
7. www.pubmed.com

What Factors Can Predict the Success of Sacroneuromodulation When Used in Patients with Urinary Retention



Introduction: Sacroneuromodulation has been used for both detrusor over activity and urinary retention. The exact mechanism of action is not known for this therapy. We sought to determine if any preoperative factors could help predict better clinical outcomes in the setting of urinary retention.

Methods: We performed a retrospective chart review from 2000 to 2010 of procedures performed by three dedicated voiding dysfunction specialists. Characteristics evaluated included age, previous surgeries, neurologic diagnosis, length of retention, invasive and noninvasive urodynamic data. Operative data collected included presence of bellows response, sacral foramen used, number of leads, number of electrodes generating a response, side of lead, and complications. Postoperative data included Subjective and objective improvement, progression to IPG implantation, wound infection, complications and need for revision.

Results: We identified 54 patients that had undergone 73 sacroneuromodulation lead placements as treatment for urinary retention (17 male, and 35 female). Mean age was 50 years. Twenty seven patients had data on length of retention with a mean of 34 months. Twenty four patients had undergone previous surgery and 18 were on medical management. All patients underwent urodynamic testing and demonstrated little or no detrusor contraction, low flows and elevated post void residuals (PVR). Mean detrusor pressure was 12.5cm/H₂O, mean flow rate was 4cc/sec and mean PVR was 593cc. Only 3 patients presented with a neurologic diagnosis. All 73 lead placements demonstrated a good bellows response. Thirty six leads were placed in the left and 36 on the right one was not recorded. Bilateral stimulation was tested in 67 patients. A mean of 2.4 electrodes generated a response after lead implantation. Subjective improvement was noted after 48 lead placements and 47 went on to implantable pulse generators (IPG). Twenty six lead placement procedures did not go on to IPG. When comparing the procedures that failed to go on to IPG versus those that did we found few differences. The mean age was higher in the failure group 55 vs. 43 years. Mean PVR was also found to be higher in the failure group 613cc versus 570cc. No difference was noted in mean flow rate, max detrusor pressure, or number of stimulating electrodes.

Conclusions: The preoperative and intraoperative factors we evaluated do not appear to give us significant prognostic data. Just as we do not fully understand the mechanism of action of this treatment the factors that may portend its success or failure have yet to be fully defined.

Introduction

The bladder is important organ that stores and expels urine. It is composed of two muscles: the detrusor muscle and sphincter muscles. The detrusor is the muscle that lines the wall of the bladder and acts like a sac that stores and empties urine. The muscle relaxes to allow your bladder to fill and contracts when it is time to expel the urine. The sphincter muscle has two parts: an internal and external muscle. The internal sphincter is a ring of muscles that open and close the neck of the bladder involuntarily. The external sphincter or distal sphincter is the “cap” that keeps the urine in the bladder. This muscle is under voluntary control via the pudendal nerve and is voluntary. When these muscles become damaged, voiding dysfunction can occur and affect quality of life. Lower urinary tract dysfunction can manifest as incontinence or urinary retention. Urinary incontinence is the involuntary leakage of urine and urinary retention is the inability to void. To define the specific cause of a patient's voiding dysfunction a physician will perform video urodynamics. This is administered to gather objective data that can be used to counsel patients about possible treatment options. Urodynamics “involves the electronic recording of the urinary flow rate throughout the course of micturition and is commonly used in patients who present with symptoms of” or urinary retention or incontinence (Urology, 9th ed., Ch. 87). In urodynamics study a “tiny catheter is inserted into the bladder as well as a tiny catheter inserted into the rectum. This measures the pressure within the bladder and the "abdominal cavity." Fluid is slowly instilled into the bladder to diagnose the pressure as the bladder fills as well as the pressure when urinating. This "bladder pressure" determination can be very helpful in accurately diagnosing the severity of neurogenic bladder and voiding dysfunction. In addition, urodynamics may be used to provide a risk assessment of a patient's potential for kidney damage and worsening symptoms over the ensuing years” (Uroassociates). This test also produces a post void residual number (PVR), which is the volume of fluid remaining in the bladder immediately after the completion of micturition. Very high PVR volumes are an indication of retention or incomplete bladder emptying. A neurogenic bladder is the result of damage to the neuronal control or efferent or afferent innervations of the bladder. This may result in retention of detrusor overactivity. In the case of urinary retention catheter is often required to adequately empty the bladder. There are several treatment options, but we will explore electrical stimulation and specifically sacral neuromodulation.

Electrical stimulation of the bladder is not a new treatment option. Unfortunately there is not substantial information about it because there is limited understanding of the complex coordination required for detrusor function. Brindley was the first to experiment with sacral root stimulation as a treatment option for incontinence in paraplegic patients. Brindley sacral anterior root stimulator uses electrical stimulation to empty the bladder, and bladder overactivity is abolished by transection of sacral dorsal roots. “Evolving data showed that for optimal bladder emptying to be achieved, sacral anterior root stimulation with posterior rhizotomies of S2, S3, and S4 would be required. The posterior rhizotomy would decrease the reflex activity of the detrusor and improve bladder compliance” (Campbell 2148). From the work of Brindley sacral neuromodulation was developed. Knowledge of this type of electrical stimulation is still evolving, but two theories exist to explain its method of action: “1) direct activation of efferent fibers to the striated urethral sphincter reflexively causes detrusor relaxation and 2) selective activation of afferent fibers causes inhibition at spinal and supraspinal levels” (Campbell 2149). Sacral neuromodulation involves the implantation of a pacemaker like device in the pelvic region to deliver low amplitude electrical impulses to S3 or S4 roots via multi electrode lead. These electrical impulses help patients with urinary retention, and urinary incontinence by restoring control of the detrusor and sphincter muscles. The constant current helps relax an overactive detrusor or influence an inactive detrusor which in turn help improves quality of life.

Due to the limited information on the mechanism of action of electrical stimulation, there is currently no significant indicator or specific test that delineates which patients will have better clinical outcomes in the setting of urinary retention. We evaluated our series to see if we could identify any factors that portended a better or worse outcome with sacral neuromodulation

Materials/Procedure:

We performed a retrospective chart review from 2000 to 2010 of procedures performed by three voiding dysfunction specialist. Characteristics evaluated included age, previous surgeries, neurologic diagnosis, length of retention, invasive and noninvasive urodynamic data. Operative data collected included presence of bellows response, sacral foramen used, number of leads, number of electrodes generating a response, side of lead, and complications. Postoperative data included subjective and objective improvement, progression to IPG implantation, wound infection, complications and need for revision.

Data/Results:

We identified 54 patients that had undergone 73 sacroneuromodulation lead placements as treatment for urinary retention 17 male, and 35 female. Mean age was 50 years. Twenty seven patients had data on length of retention with a mean of 34 months. Twenty four patients had undergone previous surgery and 18 were on medical management. All patients underwent urodynamic testing and demonstrated little or no detrusor contraction low flows and elevated post void residuals (PVR). Mean detrusor pressure was 12.5cm/H₂O, mean flow rate was 4cc/sec and mean PVR was 593cc. Only 3 patients presented with a neurologic diagnosis. All 73 lead placements demonstrated a good bellows response. Thirty six leads were placed in the left and 36 on the right one was not recorded. Bilateral stimulation was tested in 67 patients. A mean of 2.4 electrodes generated a response after lead implantation. Subjective improvement was noted after 48 lead placements and 47 went on to implantable pulse generators (IPG). Twenty six lead placement procedures did not go on to IPG.

Preoperative Mean for All Patients	
Length of Retention	34 months
UDS PVR	592.5 cc
Max Flow	4.0 cc/sec
Pressure at Max Flow	12.3 cm/H ₂ O
Evidence of Obstruction on X-Ray	43 (79%)

Preoperative Mean	Failure	Went on to InterStim Implantation
Length of Retention	24.5 months	39 months
UDS PVR	613.4 cc	570.2cc
Max Flow	4.2 cc/sec	4.1 cc/sec
Pressure at Max Flow	12.2 cm/H ₂ O	12.8 cm/H ₂ O
Evidence of Obstruction on X-Ray	14 (70%)	29 (83%)

Postoperative Statistics for All Patients	
Subjective Improvement	49 (67%)

Bladder Diary Improvement	47 (64%)
Implantation	47 (64%)
Wound Infection	6 (8%)
Complications	9 (12%)
IPG Revision	20 (27%)
Mean Follow Up	26.11 months

Postoperative Statistics	Failure	Went on to InterStim Implantation
Subjective Improvement	3 (11%)	46 (98%)
Bladder Diary Improvement	3 (11%)	44 (94%)
Implantation	0 (0%)	47 (100%)
Wound Infection	1 (4%)	5(11%)
Complications	5 (19%)	4 (9%)
IPG Revision	0 (0%)	18 (38%)
Mean Follow Up	3.67 months	28.5 months

When comparing the procedures that failed to go on to IPG verses those that did we found few differences. The mean age was higher in the failure group 55 vs. 43years. Mean PVR was also found be higher in the failure group 613cc verses 570cc. No difference was noted in mean flow rate, max detrusor pressure, or number of stimulating electrodes.

Conclusion:

Failure was more common in patients that had an increase in PVR. Failure was more common in patient that had shorter operation times. We did not find a significant difference in sacral foramen or laterality for the number of lead responses. Despite these findings, the preoperative and intraoperative factors we evaluated do not appear to give us significant prognostic data. Just as we do not fully understand the mechanism of action of this treatment the factors that may portend its success or failure have yet to be fully defined. It is important to note that further statistical analysis and study will need to be completed on the patients in this series.

Reference

Wein, Alan J., et al. "Ch. 86 and 87." *Campbell-Walsh Urology*. 9th ed. Vol. 1. 1954. New York: Saunder, 2006. Vol. 1. *EBOOKEE*. Web. 6 Aug. 2009. <http://www.ebookee.com/Campbell-Walsh-Urology-9th-Edition_119239.html>.

De'Angelo Dinkins,

Mentors: Christina Voelkel-Johnson PhD, Helen Gosnell, Tejas Tirodkar

Redox protein expression and susceptibility to therapeutic intervention in ARCaP prostate cancer cells

Abstract

Introduction: Thioredoxin is a redox-regulating protein that plays a central role in regulating cellular redox and preventing cell death. There is a high expression of thioredoxin in cancer cells because the tumor environment is usually under either oxidative or hypoxic stress and both stresses are known to be up-regulators of thioredoxin expression. Prostate cancer is the 2nd leading cancer in men after lung cancer. Indolent disease can be treated fairly well and progresses slowly. However, the more aggressive form of prostate cancer spreads throughout the body and there are no curative treatments.

Hypothesis: We tested the hypothesis that increased expression of redox proteins is an underlying cause for the aggressive, therapy-resistant prostate cancer phenotype.

Methods: In our project we looked at the expression of redox proteins and susceptibility to chemotherapy in ARCaPe and ARCaPm cells. Using western blot methods and Image J we were able to quantify the expression of thioredoxins. Susceptibility to chemotherapy was tested in a viability assay.

Results: Western blot analysis indicated increased expression of the redox proteins such as thioredoxin 1 and thioredoxin 2 in ARCaPm cells when compared to ARCaPe cells. Our results conclusively showed that Taxol killed both cell types, while Depsipeptide proved effective on ARCaPe cells and ineffective on the ARCaPm cells. We are currently determining the effect of combination therapies.

Conclusion: In conclusion we found that ARCaPm cells do have an increased expression of redox proteins. Therefore they are more resistant to cancer treatments, such as depsiptide.

INTRODUCTION

Prostate cancer is a form of cancer that develops in the prostate. Prostate cancer tends to develop in men over the age of fifty and although it is one of the most prevalent types of cancer in men, many never have symptoms, undergo no therapy, and eventually die of other causes. Most prostate cancers are slow growing; however, there are cases of aggressive prostate cancers. The cancer cells may metastasize from the prostate to other parts of the body, particularly the bones and lymph nodes. Prostate cancer may cause pain, difficulty in urinating, problems during sexual intercourse, or erectile dysfunction. Other symptoms can potentially develop during later stages of the disease. Many factors, including genetics and diet, have been implicated in the development of prostate cancer. If there is a history of people in a family with prostate cancer there is an increased risk of prostate cancer for males in that family. Prostate cancer is also more common in African American males and less common in south an eastern Asia. The presence of prostate cancer may be indicated by symptoms, physical examination, prostate specific antigen (PSA), or biopsy. Suspected prostate cancer is typically confirmed by taking a biopsy of the prostate and examining it under a microscope. Further tests, such as CT scans and bone scans, may be performed to determine whether prostate cancer has spread. Treatment options for prostate cancer with intent to cure are primarily surgery, radiation therapy, and proton therapy. Other treatments, such as hormonal therapy, chemotherapy, cryosurgery, and high intensity focused ultrasound (HIFU) also exist, depending on the clinical scenario and desired outcome.

Apoptosis signal-regulating kinase 1(ASK1) activates the c-Jun N-terminal Kinase (JNK) in a Raf independent fashion in response to an array of stresses. It has been found to be involved in cancer. Thioredoxin is a redox

protein. Thioredoxins facilitate the reduction of other proteins by cysteine thiol-disulfide exchange. Thioredoxins are found in nearly all known organisms and are essential for life in mammals. When thioredoxin levels are up regulated cell growth and resistance to the normal mechanism of programmed cell death are increased. Increased Thioredoxin in primary cancers compared to normal tissue contributes to increased cell growth and resistance to chemotherapy. Thioredoxin offers a target for the development of drugs to treat and prevent cancer. ASK1 mediates cytokines and oxidative stress (ROS)-induced apoptosis in a mitochondria dependent pathway. ASK1 in mitochondria is JNK independent and ASK1 in cytoplasm is JNK dependent. Mutation of ASK1 at C250 enhanced ASK2 induced JNK activation and apoptosis. Trx 1 blocks ASK1 signal to JNK in cytoplasm and Trx2 inhibits ASK1 in mitochondria. ASK1 in the mitochondria is c-Jun N-terminal Kinase (JNK) dependent.

The purpose of our study was to test if increased expression of redox proteins is an underlying cause for the aggressive, therapy-resistant prostate cancer phenotype. In our project we looked at the expression of redox proteins and susceptibility to chemotherapy in ARCaPe and ARCaPm cells. With this information we can find effective treatments for aggressive prostate cancer phenotype.

METHODS AND MATERIALS

We isolated the protein from the cells. To do this we added RIPA buffer and Mammalian Protease cocktail (MPC) 5ul of Mammalian Protease cocktail for each 500ul of RIPA buffer (1:100 dilution). The tube containing cell pellet was vortex then the mixture (RIPA and MPC) was added to the cell. We stored the cell on ice for 15 minutes then vortex again. It is spun at 4C in microfuge for 20 min and then transferred into a new tube for protein assay.

NuPage gels

Heat block is turned on to 70C. Then the samples were prepared each sample was given 6ul of sample buffer and 1.5ul DTT. For marker tube 4ul of rainbow marker was prepared no more than 30ul volume or 50ug protein was added to each tube. Tubes were then put in vortex to bring all liquid to the bottom. Tubes were then set in heat block for 10 min at 70C. Spun again then kept at room temperature.

While samples were heating running buffer (760ml ddH₂O and 40ml 20x MES running buffer) was prepared. 600ml of running buffer was poured into outer chamber of gel box. 500ul of antioxidant was then added to remaining 200ml of buffer and poured into inner chamber gels were rinsed and samples were loaded into gel. We ran the gels for 40-50 min at 200v (4-12% NuPage). After gel is ran 400 ml of transfer buffer was prepared. This consisted of 300 ml of ddH₂O, 20 ml of 20x transfer buffer 80 ml of MeOH and 400 ul of antioxidant. Next we assembled a transfer unit to assemble the transfer unit pads were soaked in transfer buffer and we wet nitrocellulose paper with ddH₂O placed two pads into deep side of transfer unit disassembled the gel placed one piece of 3MM paper onto the gel pushed gel out and placed it 3MM side down onto pads in transfer unit. Next nitrocellulose was put onto the gel and topped with another piece of 3MM paper. Then the rest of the transfer unit was filled with pads until 5mm over edge of transfer unit. Transfer unit was closed and placed in gel box. Buffer was added to the inner chamber and water was added to the outer chamber. Gel was transferred at 30v for 1.5 hr.

When transfer is completed the blot was blocked by placing nitrocellulose into 5% milk in TBS-Tween(TBS with 0.1% Tween) in a 50 ml conical tube and was allowed to rotate for at least 30 min at room temperature. The blot is then put in primary antibody (Trx1, Trx2, Catalase, DJ-1, or GAPDH) overnight at 4C. Blot is then washed 3 times for 10 min with TBS-Tween. Then they were put in secondary antibody for 1-2 hours at room temperature. Washed 3 times for 10 min in TBS-Tween. The blot is then put in 750 ul of each supersignal DuraWest (pierce) reagent for 5 min. The blot was then placed into a film cassette and exposed in a darkroom.

NIH Image

This was used to quantify the western blot signals. Blot was taken to an imager and image was converted to jpg. Then we opened NIH (Image J) we drew boxes around all of the lanes 1 box per lane. Then we analyzed the gels which made plots of the bands. Then we sectioned off each peak and quantified the results. The results were in turn pasted into excel where we generated graphs of our results.

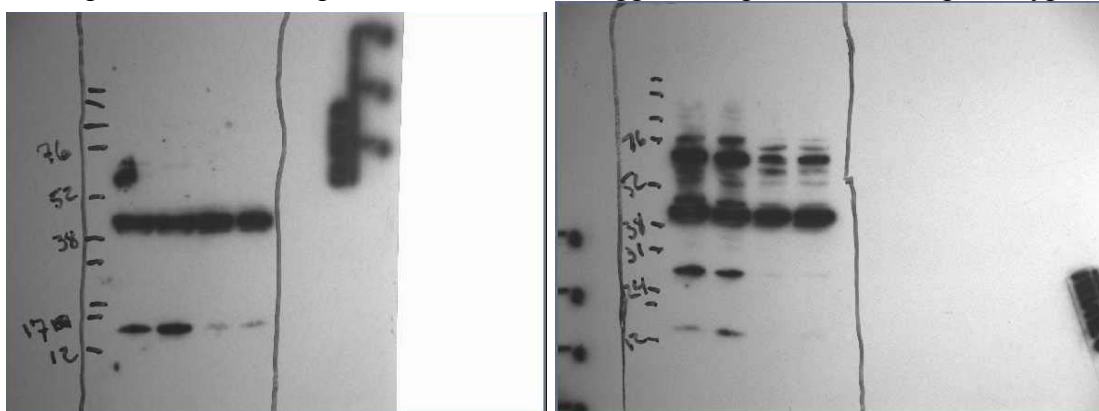
MTS Assay

Cells were plated in triplet with 96-well plate and 2 hours later infected with the cells with the proper titer of virus. 24 hours after infection, medium is replaced with 100ul fresh medium, and 20ul of Cell Titer 96 Aqueous One Solution (Promega, Cat.#: G3582) added. A triplet “no-cell” control containing 50ul of culture medium and 25ul of each Solution at the same time. Return the plate to incubator for 48 to 72 hours. Empty each well of a 96-well plate, and record fluorescence with a 96-well plate reader. Subtract the average fluorescence from the “no-cell” control from all other fluorescence values yields the corrected fluorescence.

RESULTS

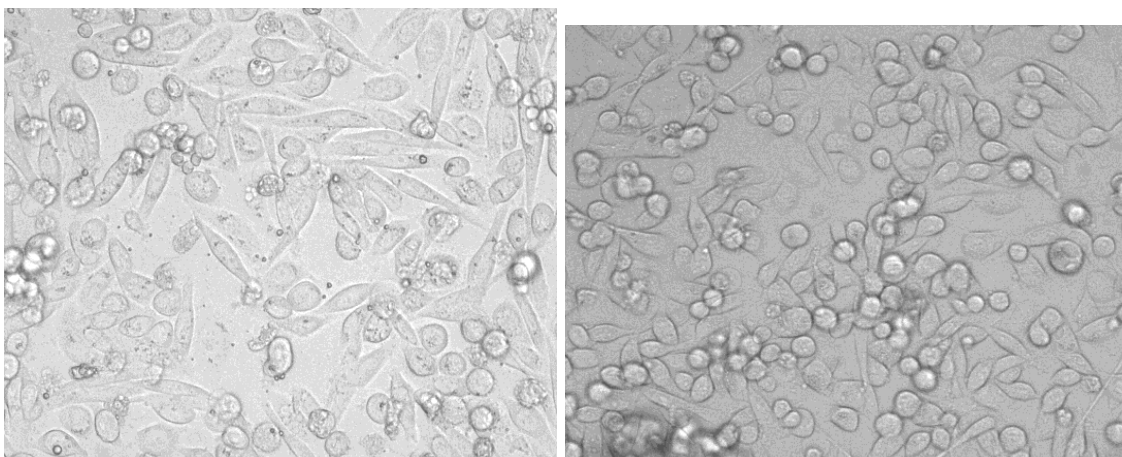
Increased expression of redox protein in ARCaPm cells

We used western blot and compared ARCaPe cells next to ARCaPm cells. After the blots were quantified using Image J we could see an increase expression of our redox proteins in the ARCaPm cells. This confirms that redox proteins are more prevalent in the more aggressive prostate cancer phenotype.



Effects of Taxol and Depsipeptide on cancer cells independently

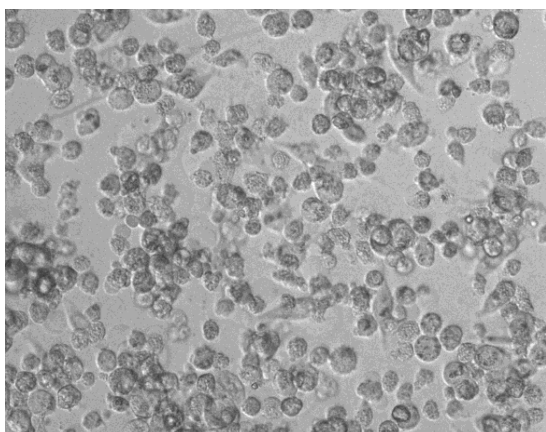
To investigate the possible effect of Taxol a chemotherapy drug on prostate cancer cells. We did a MTS assay and plated ARCaPe and ARCaPm cells on a 96 well plate and cells were treated with increasing concentrations of Taxol and Depsipeptide. Plates were let in incubator for 48 hr. The fluorescence readings show that Taxol was effective on both ARCaPe and ARCaPm cells but in very high concentrations the readings also show that Depsipeptide is effective in ARCaPe but not effective in ARCaPm.



(Left Depsipeptide 200μM ; Right 5μM Taxol)

Effects of Taxol and Depsipeptide on cancer cells in combination

To examine the effects of Taxol and Depsipeptide on ARCaP cells. A MTS assay was run. One plate ARCaPe cells and another plate ARCaPm cells. Cells were treated with increasing concentrations of taxol from left to right and increasing concentrations of Depsipeptide top to bottom. After 48 hrs reading were taken for fluorescence readings show that the two drugs can work together to kill prostate cancer cells



The two drugs are shown here working together to kill ARCaPm cells.

CONCLUSION

So both cell lines are sensitive to taxol (at very high and probably not clinically relevant concentrations). ARCaPe displays some sensitivity to Depsipeptide and ARCaPm do not. This shows a correlation between increased thioredoxins and Depsipeptide not working. This gave a reason to test for synergy and possible combination therapy when the two works together they work very well together to kill the prostate cancer cells.

REFERENCES

- ^ Hattori K, Naguro I, Runchel C, Ichijo H (2009). "The roles of ASK family proteins in stress responses and diseases". *Cell Commun. Signal* 7: 9.
- ^ Fujino G, Noguchi T, Matsuzawa A, *et al.* (December 2007). "Thioredoxin and TRAF family proteins regulate reactive oxygen species-dependent activation of ASK1 through reciprocal modulation of the N-terminal homophilic interaction of ASK1". *Mol. Cell. Biol.* 27 (23): 8152–63
- ^ Nordberg J, Arnér E (2001). "Reactive oxygen species, antioxidants, and the mammalian thioredoxin system". *Free Radic Biol Med* 31 (11): 1287–312.

Name: Ebonie M. Fuller

Mentor: Marvella E. Ford, PhD

Evaluating an Intervention to Improve Perceptions of Cancer Clinical Trials among Racially Diverse Communities in South Carolina

Abstract

Objective. To conduct a cancer clinical trials education intervention with racially diverse groups in South Carolina.

Methods. The study was conducted at ten different sites in eight counties in South Carolina. The intervention consisted of a 30-minute cancer clinical trial educational presentation. Participants were recruited primarily by community partners. Pre- and post-intervention surveys were administered. The survey instrument included seven items. Sample items included the following: “Do you think that patients should be asked to take part in medical research?” and “Would you be prepared to take part in a study where treatment was chosen at random?” Analyses were completed using SPSS 16.0, SAS 9.1.3, and R v2.6.1.

Results. The study sample consisted of 195 predominantly African American participants (n=195). The majority of the 190 participants who reported age were 50+ years (57.4%). Among those who reported income (n=182), 66.6% had an annual household income < \$60,000. For each of the seven survey items assessing perceptions of cancer clinical trials, respectively, 9%, 24%, 38%, 20%, 18%, 14% and 13% of the participants changed to more favorable responses on the post-test vs. pre-test ($p<0.001$).

Conclusions. Providing cancer clinical trials information to racial and ethnic minorities led to more positive perceptions of cancer clinical trials. Future research studies could incorporate a longer follow-up period to assess the behavioral impact of the intervention and whether short-term gains are sustained over time.

Introduction

South Carolina (SC) ranks among the top 20 states in the U.S. with the highest number of cancer deaths, and one of five South Carolina residents will be diagnosed with cancer¹ during their lifetime. African Americans in South Carolina have significantly higher cancer rates than European Americans in the state.^{1,2} Breast cancer mortality rates are 1.4 times higher for African Americans than European Americans (31.5 compared to 21.9); cervical cancer rates are 2.2 times higher (4.4 compared to 2.0); colorectal cancer rates are 2.1 times higher (35.8 compared to 17.4); and prostate cancer rates are 2.3 times higher (52.4 compared to 22.7).

Underrepresentation of African Americans in Clinical Trials

Despite their higher incidence and mortality of cancer relative to their European American counterparts, African Americans are not well represented in cancer clinical trials.^{3,4} These trials provide opportunities to test new screening techniques, therapies, and biomarkers that could reduce cancer disparities. While trial participation is of major importance for all people with cancer, it is of particular importance for African Americans. Proper sampling of a heterogeneous population to ensure sample representativeness is a key component of valid epidemiologic and clinical research. Without adequate numbers of African Americans in clinical trials, the generalizability of study results to members of this population is in question.^{5,6}

Enhancing Knowledge of Clinical Trials in Diverse Communities

The need to expand the knowledge base of clinical trials among diverse community members is underscored by Ford et al.⁷ These investigators reviewed 65 studies focusing on recruitment of minorities to cancer clinical trials. They found that lack of education about cancer clinical trials was the most frequently reported barrier to participation.⁷ Other barriers included lack of culturally appropriate information about cancer clinical trials and lack of cancer knowledge. Similarly, Giuliano et al.⁸ report that lack of knowledge about clinical trials, and negative perceptions of them, are formidable barriers to the participation of minorities in clinical trials. McCaskill-Stevens et al.⁹ recommend the use of culturally appropriate educational materials to increase minority clinical trial participation.

Along the same lines of reasoning, Fallowfield et al.¹⁰ note that recruitment difficulties often arise from potential participants' concerns about ethical issues in research, as well as concern about whether the best available treatment would be given. Additionally, lack of understanding of the value of clinical trials and the randomization procedure could lead to suspicion of trials and low rates of trial participation.¹⁰

Methods

We hypothesized that increased knowledge about cancer clinical trials would lead to more positive perceptions of trials among the study participants; therefore, we conducted a cancer clinical trials education intervention with diverse populations in South Carolina.

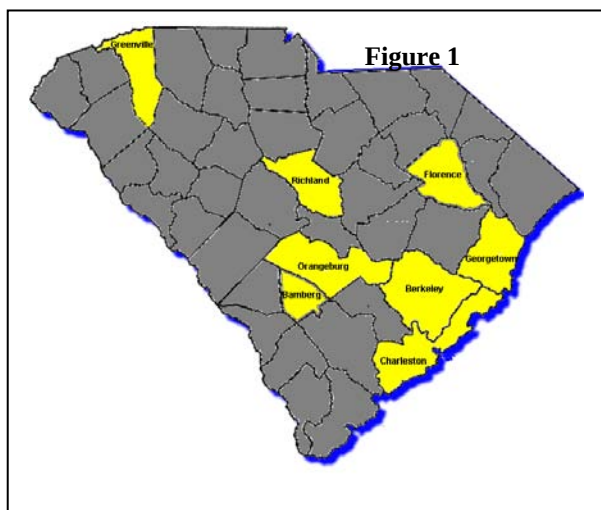
Study Sample

Our study included a convenience sample of community participants in communities with high racial disparities in cancer mortality rates. Although most of the community leaders who took responsibility for recruiting participants to the intervention were African American, we did not exclude other participants. For example, while we focused on African Americans, the racial group with the largest cancer mortality disparities in the state, we also included Native Americans and Caucasians. We did not exclude members of groups other than African Americans from taking part in the intervention.

Study participants were recruited via community partners in each locale where the training sessions were conducted. Each locale had a self-identified "champion", a community leader who took the responsibility for recruiting participants to the session. In addition, we gave presentations to patients and community members at sites during events hosted by the community partners, such as men's fellowship meetings or health ministry

meetings. We also posted flyers in community venues such as health care centers, churches, libraries, and community centers and we posted information about the sessions in local barbershops and beauty salons. Additionally, we made presentations about the sessions at meetings of fraternities, sororities and civic groups. Public service announcements on local radio stations to advertise the upcoming sessions were also made.

To enhance the representativeness of our statewide study sample, we conducted the intervention in eight different counties representing several different geographic regions of the state. These eight counties include: Berkley Georgetown, Charleston, Greenville, Orangeburg, Richland, Bamberg and Florence counties. The Ridgeville site is in Berkeley County, the Georgetown site is in Georgetown County, the Charleston and Johns



Island sites are in Charleston County, the Greenville site is in Greenville County, the Orangeburg sites are in Orangeburg County, the Columbia site is in Richland County, the Denmark site is in Bamberg County, and the Florence site is in Florence County. Three sessions were held at historically black colleges/universities (HBCUs) in Orangeburg and Bamberg Counties (Figure 1).

The sites consisted of a community cancer center (Charleston), a community center of a church (Georgetown), community health systems (Greenville, Columbia and Florence), HBCUs (two Orangeburg sites and one Denmark site), and community centers (Johns Island and Ridgeville).

Table 1. Age-Adjusted Cancer Mortality Rates for the Intervention Counties*

2006 Cancer Mortality Rate Age Adjusted Rates: 2000 US standard population Intervention Counties in South Carolina								
Race	Berkeley	Charleston	Georgetown	Greenville	Orangeburg	Richland	Bamberg	Florence
Caucasian	197.83	176.89	179.93	171.77	180.38	190.19	#	180.6
African American	206.16	222.10	187.23	244.71	261.08	237.20	291.4	226.7

*South Carolina Department of Environmental Control website (<http://www.scdhec>); accessed 7/10/09

#: Cells with 15 or fewer cases do not have rates due to the instability of small numbers when calculating rates.

The counties were selected based on their high rates of cancer disparities. Table 1 illustrates age adjusted cancer mortality rates in South Carolina for African Americans and European Americans for the counties in which we conducted the intervention.

Institutional Review Board Approval

The Institutional Review Board (IRB) at the Medical University of South Carolina approved the study protocol. The pre- and post-intervention surveys that were completed by each participant were linked by an identifier that was not connected to their name, date of birth, or any other personal identifier. The investigators had no way of connecting survey responses to individual participants in the sessions.

Design of the Cancer Clinical Trials Education Intervention

The intervention consisted of a 30-minute interactive PowerPoint presentation that is available on the National Institutes of Health (NIH)/National Cancer Institute (NCI) website. The intervention was part of a larger 3.5-hour education program aimed at increasing general cancer knowledge, prostate cancer knowledge, and perceived self efficacy in patient-physician interaction among minority populations in South Carolina.

The rationale for the dual focus of the intervention is based on cancer mortality data from South Carolina. For every major cancer, the state ranks among the highest in the nation in cancer mortality and there are large racial disparities within these cancer subtypes. For these reasons, we felt that gaining increased knowledge about many different cancer subtypes was important.

The NIH/NCI clinical trials presentation was modified to include additional pictures of African Americans and cancer mortality data that are specific to African Americans in South Carolina. Other modifications included the addition of information about the Tuskegee Syphilis Study. The intervention includes a description of which elements of the Tuskegee Syphilis Study violated human rights (e.g., not informing participants that they were in a research study; not sharing information about the modes of transmission of syphilis with infected study members; not allowing infected study members to have access to penicillin when it was discovered in the 1950s as a treatment for syphilis; not allowing the study participants to withdraw from the study at their discretion, etc.) and a description of the human subjects protections that are currently in place as a result of the Tuskegee Syphilis Study.¹¹ It also includes graphic images to illustrate the processes of random selection and randomization. The intervention was designed to present complex information in an understandable manner using simple, lay language that had meaning for the participants.

Measures

The 7-item Fallowfield instrument¹⁰ was used to assess perceptions of cancer clinical trials. The items include the following: (1) Do you think that patients should be asked to take part in medical research? (2) ...Would you be prepared to take part in a study comparing different treatments? (3) ...Would you be prepared to take part in a study where treatment was chosen at random? (4) ...Doctors and experts in the field do not know for sure if one treatment is better than the other, or if they are both the same, that's why they want to do the study. Would knowing that encourage you to take part? (5) ...In a random choice study, if the treatment you were receiving did not suit you for any reason, you could leave the study. Would that encourage you to take part? (6) ...The doctor would tell you all about the two treatments being compared before you were allocated to one or the other. Would that encourage you to take part? and (7) If you knew that ... (a) either treatment was completely suitable (b) ...you could leave the study ... (c) ...there is plenty of information... Would all these things together mean that you would change your mind and agree to take part?

Additional survey items assessed general background demographics, including Hispanic ethnicity, race, highest level of education completed, marital status, household income, age, and gender.

Statistical Methods

The survey data were double-entered into SPSS 16.0 datasets and were compared for verification of data entry. Analyses were done with SPSS 16.0, SAS 9.1.3, and R v2.6.1. Chi-square tests were used to compare demographics across all sites. Of particular interest were the percent of participants that positively changed their mind following the educational intervention. Fisher's exact tests were used to compare the number of participants that changed their mind from "No" at the pre-survey to "Yes" at the post-survey (implying a positive change) compared to the number that changed from "Yes" (pre-survey) to "No" (post-survey), which would imply a negative impact from the intervention.

Results

Table 2 shows the demographic characteristics of the participants (n=195 at pre-intervention, 94% response rate). Most participants were African American (75.4%) and most had at least a college education (75.4%). About half of the participants were married or living as married (45.1%), and the majority of participants had an annual household income $\leq$ \$60,000 (66.6%). Most participants were female (53.3%).

Table 2. Summary of Demographic of Participants at Pre-Test (N=195)		
VARIABLE	N	(%)
Age*		
Less than 50 years	78	(40.0%)
51-64 years	73	(37.4%)
65-75 years	34	(17.4%)
More than 76 years	5	(2.6%)
Hispanic*		
Yes	3	(1.5%)
No	188	(96.4%)
Race*		
African American or Black	147	(75.4%)
American Indian or Alaskan Native	15	(7.7%)
Asian	0	(0.0%)
Caucasian or White	28	(14.4%)
Pacific Islander	0	(0.0%)
Education*		
Less than 8 years	4	(2.1%)
8-11 years	8	(4.1%)
12 years or completed high school	20	(10.3%)
Post high school training other than college	12	(6.2%)
Some college	41	(21.0%)
College graduate	53	(27.2%)
Postgraduate	53	(27.2%)
Marital Status*		
Married or living as married	88	(45.1%)
Widowed	19	(9.7%)
Divorced	24	(12.3%)
Separated	5	(2.6%)
Never married	54	(27.7%)
Household Income		
\$0-\$19,999	47	(24.1%)
\$20,000-\$39,999	42	(21.5%)
\$40,000-\$59,999	41	(21.0%)
\$60,000-\$79,999	26	(13.3%)
\$80,000+	26	(13.3%)
Gender*		
Male	28	(14.4%)
Female	104	(53.3%)
*Some participants were missing data on this variable		

The demographic analysis across all sites shows a statistically significant difference in age, race, education, household income and gender (Table 3).

Table 3. Cross-Site Comparison of Demographic Characteristics of Study Participants

VARIABLE	P-VALUE
Age	0.006
Hispanic Ethnicity	0.535
Gender	0.001*
Race	< 0.001
Education	< 0.001
Marital Status	0.086
Household Income	0.019

*Gender is missing for some sites

7-Item Fallowfield Instrument Outcomes from Pre-Test to Post-Test

For many of the Fallowfield items, there was a large “yes” response at pre-test and the response remained unchanged at post-test. The majority of the participants who had less favorable perceptions of cancer clinical trials changed their perceptions from less favorable perceptions to more positive perceptions from pre- to post-test during the intervention (Table 4.) For each item, the change from pre- to post-test was statistically significant at the $p < 0.001$ level.

To use Item 1 as an example, in response to the question “Do you think that patients should be asked to take part in medical research?” 85% of the participants’ answers remained “yes” from pre-to-post-test, while 73% of

the participants (16/22) who answered “No” on the pre-test changed their responses to “Yes” on the post-test. In contrast, only 3% of participants (5/151) changed their responses from “Yes” on the pre-test to “No” on the post-test ($p < 0.001$) (Table 4.).

Table 4. Seven-Item Fallowfield Perceptions of Cancer Clinical Trials Outcomes from Pre-Test to Post-Test			
FALLOWFIELD ITEMS	POST-TEST		PRE-TEST
1. Do you think that patients should be asked to take part in medical research? (N=178)	Yes	No/DK	
	Changed Mind	5 (2.8%)	16 (9.0%)
	Did Not Change Mind	151 (84.8%)	6 (3.4%)
2. ... Would you be prepared to take part in a study comparing different treatments? (N=177)	Yes	No/DK	
	Changed Mind	6 (3.4%)	42 (23.7%)
	Did Not Change Mind	106 (59.9%)	23 (13.0%)
3. ... Would you be prepared to take part in a study where treatment was chosen at random? (N=177)	Yes	No/DK	
	Changed Mind	1 (0.6%)	67 (37.9%)
	Did Not Change Mind	47 (26.6%)	62 (35.0%)
4. ... Doctors and experts in the field do not know for sure if one treatment is better than the other, or the same, that's why they want to do the study. Would knowing that encourage you to take part? (N=118)	Yes	No/DK	
	Changed Mind	9 (7.6%)	24 (20.3%)
	Did Not Change Mind	56 (47.5%)	29 (24.6%)
5. In a random choice study, if the treatment you were receiving did not suit you for any reason, you could leave the study. Would that encourage you to take part? (N=143)	Yes	No/DK	
	Changed Mind	7 (4.9%)	25 (17.5%)
	Did Not Change Mind	93 (65.0%)	18 (12.6%)
6. ...The doctor would tell you about the two treatments being compared before allocating you. Would that encourage you to take part? (N=146)	Yes	No/DK	
	Changed Mind	4 (2.7%)	20 (13.7%)
	Did Not Change Mind	99 (67.8%)	23 (15.8%)
7. If you knew that ... (a.) either treatment was completely suitable, (b) you could leave the study ... and (c) there is plenty of information... Would all these things together mean that you would change your mind and agree to take part? (N=144)	Yes	No/DK	
	Changed Mind	5 (3.5%)	19 (13.2%)
	Did Not Change Mind	104 (72.2%)	16 (11.1%)

* $P < 0.001$

Limitations

In the present study, the assessment time period was short. We did not evaluate whether changes in perceptions of clinical trials were sustained over time. A large percentage of the participants answered “yes” at pre-test on the survey questions, so there is a type of “ceiling effect.” Future studies could incorporate a longer-term follow-up period. Additionally, the behavioral impact of the intervention could be evaluated in a future study. For example, future studies could assess whether the participants changed their willingness to enroll in a clinical trials registry and whether they actually enrolled.

Discussion

The purpose of this study was to conduct a community-based cancer clinical trials education intervention to enhance perceptions of trials among predominantly minority populations in South Carolina. Despite some limitations, the study has a number of strengths. First, the study sample included statewide representation. Second, we used a community-based recruitment strategy. We primarily relied on community representatives to recruit participants for each session. The community representatives also identified the community venue for each session. Pre- and post-intervention data show highly statistically significant increases in positive perceptions of cancer clinical trials.

Barriers to Participation of Minorities in Cancer Clinical Trials

Swanson and Ward developed a conceptual framework to describe barriers to minority cancer clinical trials participation.¹² In the framework, sociocultural barriers are described. These barriers refer to fear and mistrust of federally sponsored research, the investigators conducting the research, and/or the institutions at which the research is conducted. Negative feelings may stem from previous encounters or from hearing reports of others’ previous encounters with research studies.¹¹ Sociocultural barriers to recruitment of African Americans into clinical trials also include racial and ethnic discrimination, cultural beliefs regarding illness and disease, mistrust of the health care system, and differences in health beliefs and practices.^{12,13}

A crucial sociocultural barrier is knowledge of the Tuskegee Syphilis Experiment, in which African American men diagnosed with syphilis went untreated for research purposes. Fear of undergoing similar mistreatment prevents many African Americans from participating in current research studies.¹²

In our study, we addressed sociocultural barriers by employing the following methods. First, we conducted the intervention in trusted community venues. Second, we worked with trusted community leaders who endorsed the study and helped to recruit participants to each study session. Third, the majority of our study team members is African American and thus, reflects the racial background of the population that was recruited. Fourth, as part of the intervention, we acknowledged past clinical trial abuses in the Tuskegee Syphilis study but described how new protections for study participants came about as a result of these past atrocities.

Conclusion

Providing cancer clinical trials information to racial and ethnic minorities led to more positive perceptions of cancer clinical trials. Future research studies could incorporate a longer follow-up period to assess the behavioral impact of the intervention and whether short-term gains are sustained over time.

It is important to note that all of the participants in the cancer clinical trials education intervention received materials that they could use to conduct their own cancer clinical trials education training programs. The rationale for disseminating these materials was to assist participants in sharing cancer clinical trials information with others in their own communities. Table 5 shows that to date, 104 sessions have been conducted by 40 trained community/lay facilitators, reaching 3,292 community members. In a future study, we will evaluate the intervention outcomes from the sessions that were conducted by the trained community members.

Table 5. Cancer Education Training Sessions Conducted by Lay Facilitators			
Site	# Facilitators who Conducted Cancer Education Training Programs	# Training Programs Conducted	# Community Attendees at Each Program
Georgetown (n= 15)	8	25	702
Ridgeville (n=24)	2	2	25
Charleston (n= 17)	8	13	225
Greenville (n= 19)	10	45	1812
Orangeburg (n= 22)	1	1	15
Columbia (n= 20)	2	2	44
Orangeburg (n= 15)	0	0	0
Johns Island (n=12)	9	16	469
Denmark (n=14)	**	**	**
Florence (n=15)	**	**	**
TOTAL	40	104	3,292

** Training sessions were conducted too recently to be evaluated

References

1. South Carolina Community Assessment Network: Cancer Mortality. <http://scangis.dhec.sc.gov/scan/cancer2/mortinput.aspx>. Accessed 06/05/08.
2. South Carolina Department of Environmental Control: Age-Adjusted Rates: 2000 US standard population. <http://www.scandhec.org>. Accessed 07/10/09.
3. Ford JG, Howerton M. The science of recruiting minority populations to screening trials. *Clin Trials*. 2004;1(4):341-342.
4. Lai GY, Gary TL, Tilburt J, et al. Effectiveness of strategies to recruit underrepresented populations into cancer clinical trials. *Clin Trials*. 2006; 3(2):133-141.
5. Ford ME, Havstad SL, Davis SD. A randomized trial of recruitment methods for older African American men in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. *Clin Trials*. 2004;1(4):343-351.
6. Ford ME, Havstad SL, Tilley BC. Recruiting older African American men to a cancer screening trial (the AAMEN Project). *Gerontologist*. 2003;43(1):27-35.
7. Ford ME, Havstad SL, Fields ME, Manigo B, McClary B, Lamerato L. Effects of baseline comorbidities on cancer screening trial adherence among older African American men. *Cancer Epidemiol Biomarkers Prev*. 2008;17(5):1234-1239.
8. Giuliano AR, Mokuau N, Hughes C, et al. Participation of minorities in cancer research: the influence of structural, cultural, and linguistic factors. *Annals of epidemiology*. 2000;10(8 Suppl):S22-34.
9. McCaskill-Stevens W, Pinto H, Marcus AC, et al. Recruiting minority cancer patients into cancer clinical trials: a pilot project involving the Eastern Cooperative Oncology Group and the National Medical Association. *J Clin Oncol*. 1999;17(3):1029-1039.
10. Fallowfield LJ, Jenkins V, Brennan C, Sawtell M, Moynihan C, Souhami RL. Attitudes of patients to randomised clinical trials of cancer therapy. *Eur J Cancer*. 1998;34(10):1554-1559.
11. Thomas SB, Quinn SC. The Tuskegee Syphilis Study, 1932 to 1972: implications for HIV education and AIDS risk education programs in the black community. *Am J Public Health*. 1991;81(11):1498-1505.
12. Swanson GM, Ward AJ. Recruiting minorities into clinical trials: toward a participant-friendly system. *J Natl Cancer Inst*. 1995;87(23):1747-1759.
13. Freimuth VS, Quinn SC, Thomas SB, Cole G, Zook E, Duncan T. African Americans' views on research and the Tuskegee Syphilis Study. *Social science & Medicine*. (1982) 2001;52(5):797-808.

APPENDIX E
Student Fellows' PowerPoint Presentations

NOV-002 Induces S-Glutathionylation of Serpin A1 and A3 in Human Serum

Jonathan L. Brown
Junior, Claflin University
MUSC Hollings Cancer Center

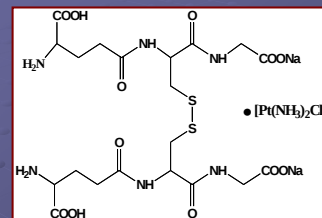
Objective

- Identify the S-Glutathionylation patterns of serpins in plasma from cancer patients via Western blot analysis
- Determine the significance that the S-Glutathionylation patterns discovered possess in relation to a cancer patient's myeloproliferation status

Hypothesis

The addition of NOV-002 to plasma samples of cancer patients will affect the glutathionylation patterns of Serpin A1 and A3.

NOV-002



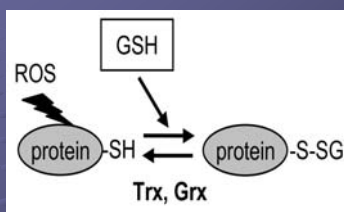
NOV-002:
Novelos Therapeutics, Inc.

•Formulation of oxidized glutathione that induces protein glutathionylation

•Chemotherapeutic utilized in cancer patients to enhance the effect of chemotherapy

•Chemoprotectant that increases white blood cell (WBC) counts

Glutathionylation



- posttranslational modification of protein cysteine residues by addition of tripeptide glutathione
- The process is similar to phosphorylation in the sense that it alters protein structure and function such as the activation or deactivation of protein enzyme activity

Proteins that are S-glutathionylated belong to 6 categories

- Cytoskeletal
- Glycolysis/ energy metabolism
- Signaling
- Calcium homeostasis
- Protein folding
- Redox

Glutathionylation of proteins increases in mouse serum following NOV-002 treatment



Background of Serpins

- Make up 2% plasma proteins
- Serine protease inhibitors
- Serine proteases cleave peptide bonds in proteins
- Inactivate enzymes by binding them covalently
- Roles in hematopoietic bone marrow cell mobilization (Wrinkler 2005)

Serpin A1 (Antitrypsin)

- Most prominent serpin that makes up majority of serpins that are found in plasma proteins
- Main role is to protect tissues from enzymes of inflammatory cells

Serpin A3 (Antichymotrypsin)

- Shares 46% of its identity with Serpin A1
- Elevated levels may be a possible cause to chronic liver disease
- Serpin A3 levels may also impact age-of onset and disease duration of Alzheimer's disease

Significance of Serpin A1 and A3 in relation to this experiment

- Discovered that the glutathionylated bands from the NOV-002 treatment in mouse were of serpins A1 and A3
- Evidence shows that both Serpin A1 and A3 are involved in myeloproliferative events

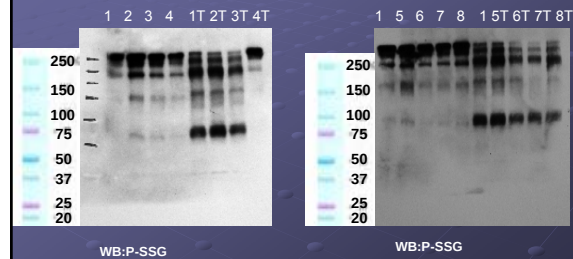
S-Glutathionylation of Serpins

- Serpins undergo S-glutathionylation after receiving NOV-002 treatment
- is promoted by oxidative and nitrosative stress but can also occurs in unstressed cells
- When serpins are S-Glutathionylated, it may prevent (blocks) serpins from binding to proteases

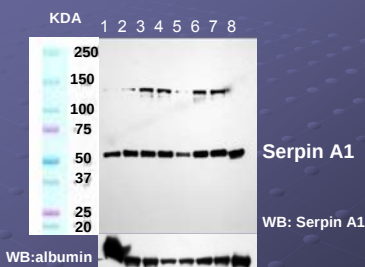
S-Glutathionylation of Serpins (Cont'd)

- After receiving NOV-002, glutathionylated Serpin A1 and A3 plays a role in myeloproliferation
- Glutathionylated serpins may prevent the inactivation of proteases that have significant roles in downstream events that affect bone marrow progenitor cell mobilization
- May result in increase of proteases involved in the hematopoietic bone marrow cell mobilization (more free proteases which normally are inactivated)

Western Blot Analysis of P-SSG



Western Blot of Serpin A1



Conclusion

- Based on the results, cancer patients have different glutathionylated Serpin A1 and A3 amounts after receiving the NOV-002 treatment
- This proves that S-glutathionylation of Serpins occur after NOV-002 which may help with hematopoietic cell mobilization in bone marrow cells
- Later studies can be conducted to better assist cancer patients and increasing their myeloproliferative status

References

- S-Glutathionylation : Indicator of Cell Stress and Regulator of the Unfolded Protein Response - Dr. Danyelle Townsend (2007)
- An Overview of the serpin superfamily - Ruby HP Law (2006)
- Serine protease inhibitors serpinA1 and serpinA3 are down-regulated in bone marrow during hematopoietic progenitor mobilization - Ingrid G. Winkler (2005)
- Serpin-A1 and A3 as potential pharmacodynamic biomarkers for NOV-002, a redox modulating anticancer agent (2010)
- Sulfiredoxin - Robert R. Bowers
- www.wikipedia.com
- www.pubmed.com

Acknowledgements

- Dr. Rebecca Bullard-Dillard, Claflin University (DOD grant)
- Debbie Shoemaker, MUSC SURP Program
- Dr. Marvella Ford, (DOD grant)
- Dr. Danyelle Townsend
- Melanie Jefferson, MPH
- Steven Hutchens
- Doctor Christina Grek
- Townsend and Tew Lab
- MUSC Hollings Cancer Center

What Factors Predict the Success of Sacro neuromodulation When Used in Patients with Urinary Retention



Presented By: Scharan Clarke
Senior, Cluffin University
S.U.R. Program Participant 2010 at MUSC
DOD Grant: Marvella Ford, PhD
MUSC Urology: Harry Clarke, MD, PhD and Matthew McIntyre, MD

Terminology

- Detrusor muscle
- Sphincter muscle
- Voiding Dysfunction
- Urinary Retention
- Urodynamics
- Sacral Neuromodulation (SNM)
 - InterStim Therapy



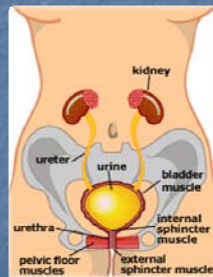
August 13, 2010

Scharan Clarke -- SURP 2010

2

Bladder Anatomy

- organ that stores and expels urine
- detrusor muscle—lines the wall of the bladder and acts like a sac that stores and empties urine
 - relaxes to allow your bladder to fill
 - contracts to expel the urine
- sphincter muscles
 - internal sphincter is a ring of muscles that open and close the bladder neck; this is under involuntary control
 - external sphincter or distal sphincter is the "cap" that keeps the urine in the bladder



August 13, 2010

Scharan Clarke -- SURP 2010

3

Voiding Dysfunction

- Voiding dysfunction refers to the inability to store urine or empty the bladder normally.
- Different types of voiding dysfunction include:
 - Incontinence— the involuntary loss of urine from the bladder. While not a normal part of the aging process, prevalence of this condition does increase with age. Types of incontinence include urge, stress, functional, overflow and transient.
 - Overactive Bladder – the layered, smooth muscle surrounding the bladder is hyperactive, resulting in involuntary contractions and the urgent need to urinate.
 - Urinary Retention – characterized by poor urinary stream with intermittent flow, straining, a sense of incomplete voiding and hesitancy (a delay between trying to urinate and the flow actually beginning).

Courtesy of: <http://www.pennmedicine.org/urology/services/incontinence.html>

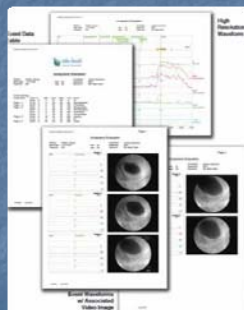
August 13, 2010

Scharan Clarke -- SURP 2010

4

Diagnosis

- Patient history is the most important step
- These steps are used to confirm diagnosis
 - Bladder Diary
 - Urodynamics
 - Post Void Residual (PVR)



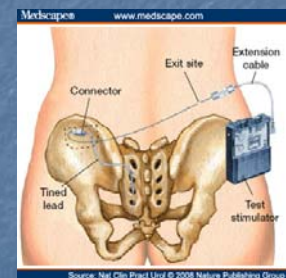
August 13, 2010

Scharan Clarke -- SURP 2010

5

Treatment: Sacral Neuromodulation (SNM)

- Sacral nerve stimulation (InterStim Therapy) is a therapy that addresses the nerve component of urinary control.
- Sacral nerve stimulation is intended for patients who have failed or could not tolerate more conservative treatments.



Source: Nat Clin Pract Urol © 2008 Nature Publishing Group

August 13, 2010

Scharan Clarke -- SURP 2010

6

History of SNM

- Brindley was the first to experiment with sacral root stimulation as a treatment option for incontinence in paraplegic patients.
 - Brindley sacral anterior root stimulator uses electrical stimulation to empty the bladder, and bladder overactivity is abolished by transection of sacral dorsal roots.
 - data showed that for optimal bladder emptying to be achieved, sacral anterior root stimulation with posterior rhizotomies of S2, S3, and S4 would be required

Theories of SNM

- Knowledge of this type of electrical stimulation is still evolving, but two theories exist to explain its method of action:
 - 1) direct activation of efferent fibers to the striated urethral sphincter reflexively causes detrusor relaxation
 - 2) selective activation of afferent fibers causes inhibition at spinal and supraspinal levels

August 13, 2010

Scharan Clarke -- SURP 2010

8

Objective

- We sought to determine if any preoperative factors could help predict better clinical outcomes in the setting of urinary retention.

August 13, 2010

Scharan Clarke -- SURP 2010

9

Methods

- We performed a retrospective chart review from 2000 to 2010 of procedures performed by three dedicated voiding dysfunction specialist.
 - Preoperative factors: age, previous surgeries, neurologic diagnosis, length of retention, invasive and noninvasive urodynamic data
 - Intraoperative factors: presence of bellows response, sacral foramen used, number of leads, number of electrodes generating a response, laterality of lead (L/R), and complications
 - Postoperative factors: subjective and objective improvement, progression to IPG implantation, wound infection, complications and need for revision and follow up

August 13, 2010

Scharan Clarke -- SURP 2010

10

Results

- We identified 54 patients that had undergone 73 sacro neuromodulation lead placements as treatment for urinary retention
 - 39 had 1 InterStim procedure
 - 13 had 2 InterStim procedures
 - 3 had 3 InterStim procedures
- 17 male and 35 female
- Mean age was 50 yrs

August 13, 2010

Scharan Clarke -- SURP 2010

11

Results cont.

- 27 patients had data on length of retention with a mean of 34 months
- 24 patients had undergone previous surgery and 18 were on medical management
- All patients underwent urodynamic testing and demonstrated little or no detrusor contraction low flows and elevated (PVR)

August 13, 2010

Scharan Clarke -- SURP 2010

12

Results: Success v. Failure

- We identified 20 patients that had undergone 26 **failed** sacroneuromodulation lead placements as treatment for urinary retention
 - 15 had 1 failed InterStim procedure
 - 5 had 2 failed InterStim procedures
- We identified 35 patients that had undergone 47 **successful** sacroneuromodulation lead placements as treatment for urinary retention
 - 27 had 1 successful InterStim procedure
 - 7 had 2 successful InterStim procedures
 - 1 had 3 successful InterStim procedures

August 13, 2010

Scharan Clarke -- SURP 2010

13

Results: Success v. Failure cont.

- Failure: 9 male and 11 female
- Success: 8 male and 27 female
- Mean age was higher in the failure group 55 vs. 43years
- Mean PVR was also found to be higher in the failure group 613cc verses 570cc
- No difference was noted in mean flow rate, max detrusor pressure, or number of stimulating electrodes.

August 13, 2010

Scharan Clarke -- SURP 2010

14

Results: Preoperative

Mean for All Patients	
Length of Retention	34 months
UDS PVR	592.5 cc
Max Flow	4.0 cc/sec
Pressure at Max Flow	12.3 cm/H ₂ O
Evidence of Obstruction on X-Ray	43 (79%)

August 13, 2010

Scharan Clarke -- SURP 2010

15

Mean	Failure	Went on to InterStim Implantation
Length of Retention	24.5 months	39 months
UDS PVR	613.4 cc	570.2cc
Max Flow	4.2 cc/sec	4.1 cc/sec
Pressure at Max Flow	12.2 cm/H ₂ O	12.8 cm/H ₂ O
Evidence of Obstruction on X-Ray	14 (70%)	29 (83%)

Results: Intraoperative

- All the patients had bellows response
 - 67 (92%) patients had both their right and left sides tested for bellows response
 - There were no complications
 - Foramen Placement:
 - 66 had S3 (90%)
 - 6 had S4 (8%)
 - 1 had S2 (2%)
 - Right or Left Foramen:
 - 36 L (49%)
 - 36 R (49%)
- NOTE: There is no mention of what side the needle was placed for 2 procedures
- Average of electrode responses: 2.44
 - Average operation time: 48.2 min

Results: Intraoperative (Failure)

- All the patients had bellows response
 - 26 (100%) patients had both their right and left sides tested for bellows response
- There were no complications
- Foramen Placement:
 - 23 had S3 (88%)
 - 3 had S4 (12%)
- Right or Left Foramen:
 - 16 L (62%)
 - 10 R (38%)
- Average of electrode responses: 2.42
- Average operation time: 23 min

August 13, 2010

Scharan Clarke -- SURP 2010

18

Results: Intraoperative (InterStim Implantation)

- All the patients had bellows response
 - 47 (100%) patients had both their right and left sides tested for bellows response
- There were no complications
- Foramen Placement:
 - 42 had S3 (89%)
 - 4 had S4 (9%)
 - 1 had S2 (2%)
- Right or Left Foramen:
 - 18 L (38%)
 - 27 R (57%)

NOTE: There is no mention of what side the needle was placed for 2 procedures
- Average of electrode responses: 2.43
- Average operation time: 43 min

August 13, 2010

Scharan Clarke -- SURP 2010

19

Results: Postoperative

Statistics for All Patients	
Subjective Improvement	49 (67%)
Bladder Diary Improvement	47 (64%)
Implantation	47 (64%)
Wound Infection	6 (8%)
Complications	9 (12%)
IPG Revision	20 (27%)
Mean Follow Up	26.11 months

August 13, 2010

Scharan Clarke -- SURP 2010

20

Statistics	Failure	Went on to InterStim Implantation
Subjective Improvement	3 (11%)	46 (98%)
Bladder Diary Improvement	3 (11%)	44 (94%)
Implantation	0 (0%)	47 (100%)
Wound Infection	1 (4%)	5(11%)
Complications	5 (19%)	4 (9%)
IPG Revision	0 (0%)	18 (38%)
Mean Follow Up	3.67 months	28.5 months

Chances of IPG Implantation After a Failed Lead Attempt

- 9 patients failed the 1st attempt and had a second procedure
- Failed/Went on to IPG Implantation: 4 (44.4%)
- Failed/Failed: 5 (55.5%)

August 13, 2010

Scharan Clarke -- SURP 2010

22

Conclusion

- Failure was more common in patients that had an increase in PVR
- Failure was more common in patient that had shorter operation times
- We did not find a significant difference in sacral foramen or laterality for the number of lead responses
- Just as we do not fully understand the mechanism of action of this treatment the factors that may portend its success or failure have yet to be fully defined.

NOTE: Further statistical analysis and study will need to be completed on the patients in this series.

August 13, 2010

Scharan Clarke -- SURP 2010

23

Acknowledgements

MUSC SURP program (Debbie Shoemaker)
 Urology Dept: Dr. Harry Clarke
 Dr. Matthew McIntyre
 DOD Grant (Dr. Marvella Ford and Melanie Jefferson)
 Claflin University (Dr. Rebecca Bullard-Dillard)

August 13, 2010

Scharan Clarke -- SURP 2010

24

Questions



"Redox protein expression and susceptibility to therapeutic intervention in ARCaP prostate cancer cells"

De'Angelo Dinkins

Dr. Voelkel-Johnson lab
Summer Undergraduate Research Program 2010
South Carolina State University

Prostate

□□□□□

- The prostate is a gland in the male reproductive system that produces the majority of fluid that makes up semen
- The walnut-sized gland is located beneath a man's bladder and surrounds the upper part of the urethra, the tube that carries urine from the bladder

QuickTime™ and a TIFF (Uncompressed) decompressor are needed to see this picture.

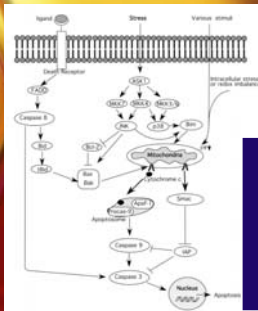
Prostate Cancer

- Prostate cancer is the 2nd leading cause of cancer death in men after lung cancer.
- More than 200,000 new cases and about 30,000 deaths are attributed to prostate cancer each year in the U.S
- It is more aggressive in African American males but is still a slow growing cancer.
- Prostate cancer is rare in Asia and high in the U.S this could be attributed to diet.
- Lots of males may die with prostate cancer but not of it.

Prostate Cancer Treatment options

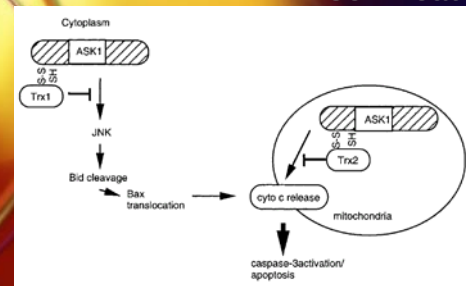
- In early stages you may just watch and see if it spreads. Also they may use radiation therapy
- But in more advanced cases they have surgery, chemotherapy, hormone therapy and radiation therapy.

Cell Death



Mol. Nutr. Food Res. 53: 87 (2009)

The Role of Thioredoxins in Cell Death



Circulation research 94:1483 (2004)

Hypothesis

- Increased expression of redox proteins is an underlying cause for the aggressive, therapy-resistant prostate cancer phenotype.

Prostate Cancer Cell Lines

- Androgen-repressed human prostate cancer cell line (ARCaP)
- ARCaPe (epithelial)
- ARCaPm (mesenchymal)

ARCaPe cells

- ARCaPE cells are human prostate cancer cells established from a parental mixed ARCaP cell population with a low propensity for bone metastasis in mice

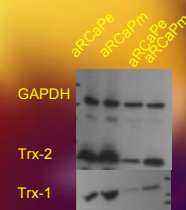
ARCaPm cells

- ARCaPM cells are human prostate cancer cells established from a parental mixed ARCaP cell population with a high propensity for bone metastasis in mice. Histopathology of the tumors that grow in bone mainly show osteoblastic lesions that recapitulate human prostate cancer bone metastasis

Methods section

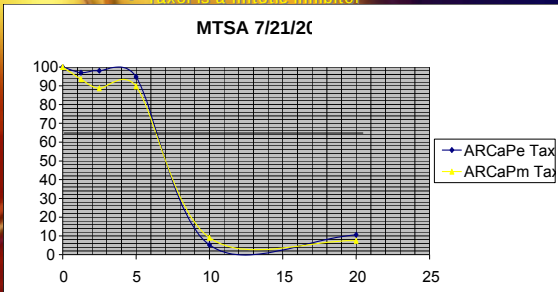
- Western blot
- MTS assay

Expression of Thioredoxins in ARCaP Cells

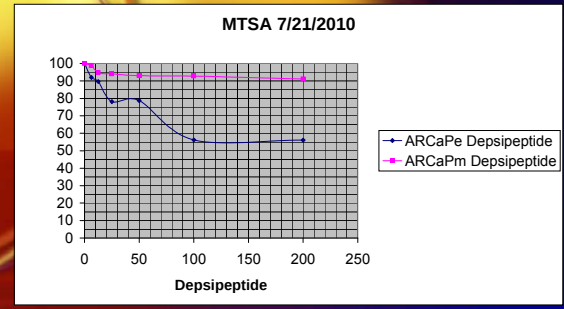


Susceptibility of ARCaP cells to Taxol

Taxol is a mitotic inhibitor



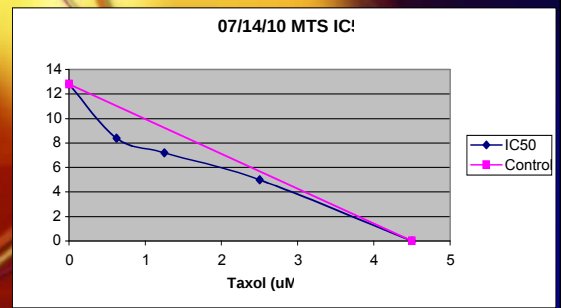
Susceptibility of ARCaP cells to Depsipeptide



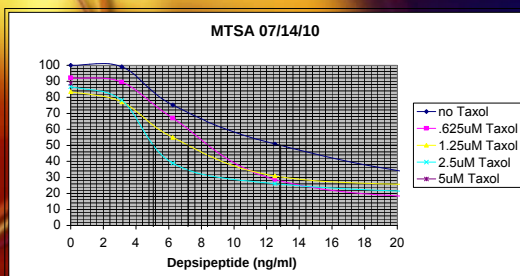
Drug Synergy

- Drug Synergy is the combination of two or more drugs to produce a result non obtainable on its own
- Two drugs might work fine alone but when combined with another drug it can be more effective and some times less effective.

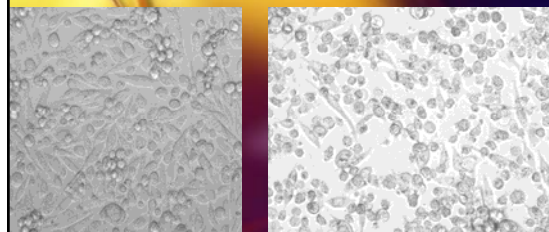
Drug Synergy (cont.)



Effects of Taxol/Depsipeptide Combination Therapy

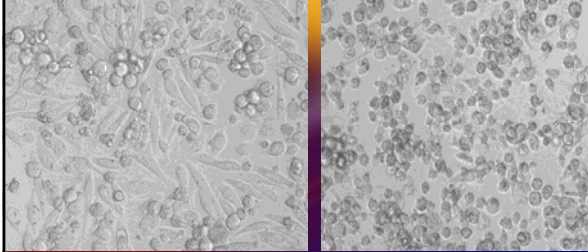


Effects of Taxol/Depsipeptide Combination Therapy



1.25 taxol with no depsipeptide, 50uM depsipeptide, and 200uM depsipeptide

Effects of Taxol/Depsipeptide Combination



Conclusions

- Our hypothesis was correct
- Increased expression of redox proteins is an underlying cause for the aggressive, therapy-resistant prostate cancer phenotype.
- This information can be used to find more treatments for prostate cancer.



Acknowledgements

- Dr. Voelkel-Johnson
- Tejas Tirodkar
- Helen Gosnell
- Dr. Marvella Ford
- Melanie Sweat-Jefferson
- SURP

Evaluating an Intervention to Improve Perceptions of Cancer Clinical Trials among Racially Diverse Communities in South Carolina

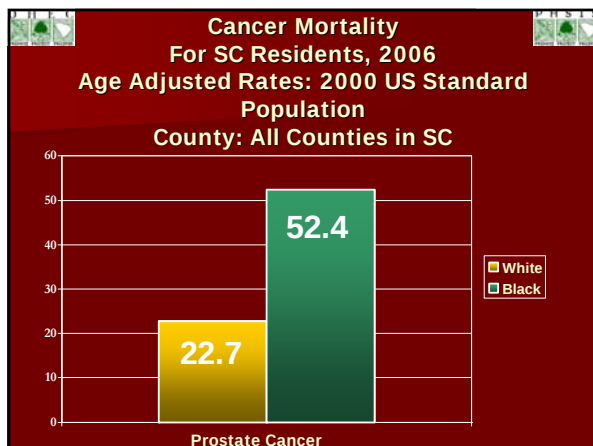
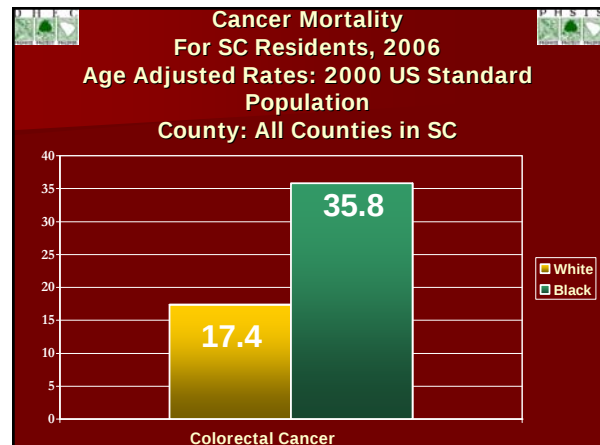
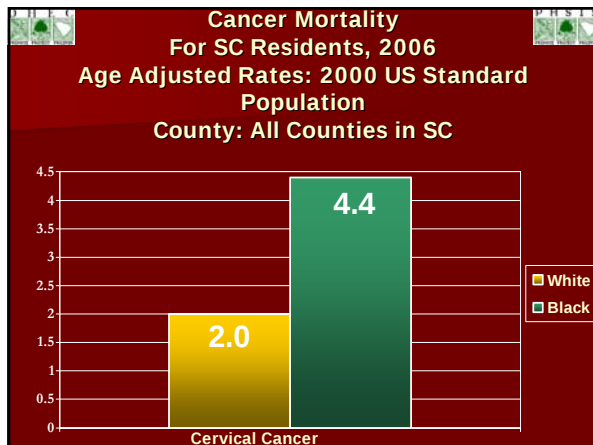
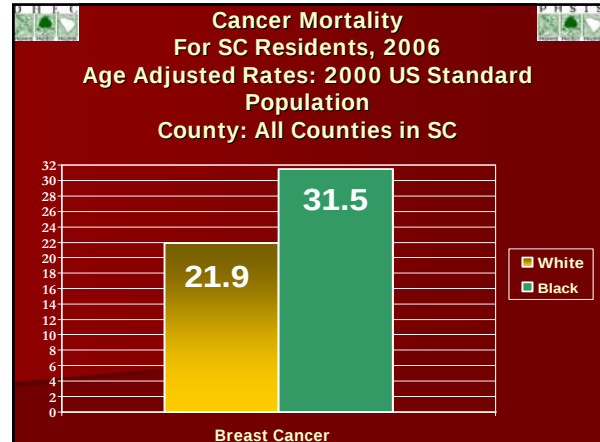


Ebonie Fuller

Junior, Biology and Spanish Student
South Carolina State University

Contributing Authors:

Rashell Blake
June Streets
Katie A. Mitchum
Mary Beth McClary
Heather Brandt, PhD
Reverend Remus Harper, Jr.
Marylou B. Stinson, MPH, MSW
Jim Etheredge, MPA
Melanie A. Sweat, MPH
Katora Campbell, MPH
Amy E. Wahlquist, MS
Marvella E. Ford, PhD



Statement of the Problem

- Despite the African American population's higher incidence and mortality of cancer, they are less likely to participate in cancer clinical trials
- Therefore, treatments may not be targeted to members of this group

Why Are Clinical Trials Important?

- Each study answers scientific questions and tries to find better ways to prevent, screen for, diagnose or treat a disease
- Responses to a treatment may differ by population, therefore testing is needed

Description of the Intervention

4-Hour Cancer Education Program

- 3-hour component focusing on general cancer knowledge
- 30-minute component focusing on prostate cancer knowledge
- **30-minute component focusing on cancer clinical trials information**

Description of the Intervention (continued)

- **Train the Trainer Model**
- A National Institutes of Health PowerPoint presentation that describes cancer clinical trials

Recruitment Strategies

We Recruited Participants by:

- Relying on community partners to recruit participants
- Giving presentations to patients and community members at the sites during events hosted by the community partners

Recruitment Strategies (continued)

We Recruited Participants by:

- Posting flyers in community venues such as health centers, churches, libraries, and community centers
- Going to barbershops, beauty salons, meetings of fraternities and sororities, and civic groups to describe the cancer education training sessions
- Making public service announcements on radio stations

Description of the Intervention (continued)

Assessment Instruments

- General sociodemographic information (e.g., age, race, income)
- Perceptions of cancer clinical trials (Fallowfield 1998)

Description of the Intervention (continued)

Assessment Intervals

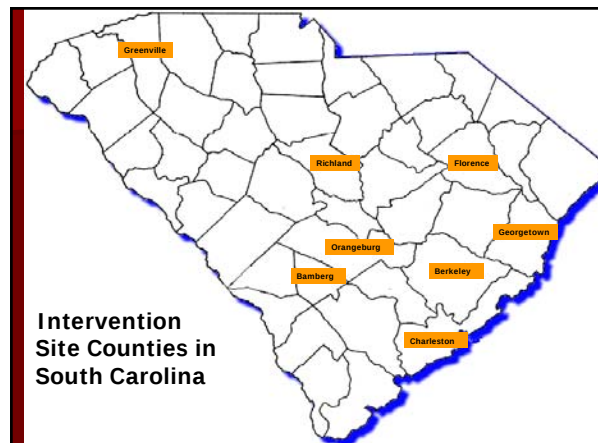
- Pre-test (immediately prior to the intervention)
- Post-test (immediately following the intervention)

Ten Intervention Sites

Study Sites	Dates	Predominant Population	Location
Ridgeville, SC	10/27/2007	Native American	Community Center
Georgetown, SC	02/09/2008	African American	Community Center
Charleston, SC	06/21/2008	African American	Cancer Center
Greenville, SC	10/25/2008	African American	Health Care Center
Orangeburg, SC (1)	11/01/2008	African American	HBCU

Ten Intervention Sites (continued)

Columbia, SC	05/09/2009	African American	Health Care Center
Orangeburg, SC (2)	5/30/2009	African American	HBCU
Johns Island	06/13/2009	African American	Community
Denmark, SC	02/27/2010	African American	HBCU
Florence, SC	03/27/2010	African American	Health Care Center



Hypothesis

The Intervention Will Positively Influence Participants' Perceptions of Clinical Trials

- Outcome: pre- / post-intervention changes in perceptions of cancer clinical trials

Statistical Methods

Results Were Calculated Using Simple Descriptive Statistics to Determine Post-Intervention Increase in:

- Positive perceptions of cancer clinical trials



Results

Variable (N=195)	N	%
Race		
African American	147	75.4
Caucasian	28	14.4
American Indian/Alaskan Native	15	7.7
Other	0	0.0
Hispanic		
Yes	3	1.5
No	188	96.4
Age		
Less than 50 years	78	40.0
51-64 years	73	37.4
65-75 years	34	17.4
More than 76 years	5	2.6

*Missing data from some participants

Results (continued)

Variable (N=195)	N	%
Household Income		
\$0-\$19,999	47	24.1
\$20,000-\$39,999	42	21.5
\$40,000-\$59,999	41	21.0
\$60,000-\$79,999	26	13.3
\$80,000+	26	13.3
Education		
Less than 8 years	4	2.1
8 through 11 years	8	4.1
12 years/completed high school	20	10.3
Post high school training other than college	12	6.2
Some college	41	21.0
College graduate	53	27.2
Postgraduate	53	27.2

*Missing data from some participants

Results (continued)

Variable (N=195)	N	%
Gender*		
Male	28	14.4
Female	104	53.3
Marital Status		
Married or Living As Married	88	45.1
Widowed	19	9.7
Divorced	24	12.3
Separated	5	2.6
Never Married	54	27.7

*Missing data from some participants

Demographic Comparisons By Site

Variable	P-Value
Age	0.006
Hispanic	0.535
Race	<0.001
Education	<0.001
Marital Status	0.086
Household Income	0.019
Gender*	0.001

*Not all sites have information regarding gender

Pre-Test and Post-Test Perceptions of Cancer Clinical Trials

1. Do you think that patients should be asked to take part in medical research?

	PRE		
	Yes N (%)	No/DK N (%)	Total
POST Changed Mind	5 (2.8)	16 (9.0)	21
Did Not Change Mind	151 (84.8)	6 (3.4)	157
TOTAL	156	22	178

p<0.001

Pre-Test and Post-Test Perceptions of Cancer Clinical Trials

2. ...Would you be prepared to take part in a study comparing different treatments?

	PRE		
	Yes N (%)	No/DK N (%)	Total
POST Changed Mind	6 (3.4)	42 (23.7)	48
Did Not Change Mind	106 (59.9)	23 (13.0)	129
TOTAL	112	65	177

p<0.001

Pre-Test and Post-Test Perceptions of Cancer Clinical Trials

3. ...Would you be prepared to take part in a study where treatment was chosen at random?

POST	PRE		
	Yes N (%)	No/DK N (%)	Total
Changed Mind	1 (0.6)	67 (37.9)	68
Did Not Change Mind	47 (26.6)	62 (35.0)	109
TOTAL	48	129	177

p<0.001

Pre-Test and Post-Test Perceptions of Cancer Clinical Trials

4. ...Doctors and experts in the field do not know for sure if one treatment is better than the other, or the same, that's why they want to do the study. Would knowing that encourage you to take part?

POST	PRE		
	Yes N (%)	No/DK N (%)	Total
Changed Mind	9 (7.6)	24 (20.3)	33
Did Not Change Mind	56 (47.5)	29 (24.6)	85
TOTAL	65	53	118

p<0.001

Pre-Test and Post-Test Perceptions of Cancer Clinical Trials

5. ...In a random choice study, if the treatment you were receiving did not suit you for any reason, you could leave the study. Would that encourage you to take part?

POST	PRE		
	Yes N (%)	No/DK N (%)	Total
Changed Mind	7 (4.9)	25 (17.5)	32
Did Not Change Mind	93 (65.0)	18 (12.6)	111
TOTAL	100	43	143

p<0.001

Pre-Test and Post-Test Perceptions of Cancer Clinical Trials

6. ...The doctor would tell you about the two treatments being compared before allocating you. Would that encourage you to take part?

POST	PRE		
	Yes N (%)	No/DK N (%)	Total
Changed Mind	4 (2.7)	20 (13.7)	24
Did Not Change Mind	99 (67.8)	23 (15.8)	122
TOTAL	103	43	146

p<0.001

Pre-Test and Post-Test Perceptions of Cancer Clinical Trials

7. If you knew that ...
a. either treatment was completely suitable
b. you could leave the study ...
c. there is plenty of information...

Would all these things together mean that you would change your mind and agree to take part?

POST	PRE		
	Yes N (%)	No/DK N (%)	Total
Changed Mind	5 (3.5)	19 (13.2)	24
Did Not Change Mind	104 (72.2)	16 (11.1)	120
TOTAL	109	35	144

p<0.001

Educational Sessions by Trained Community Members following the Cancer Clinical Trials Education Intervention

Site	Number of facilitators who conducted community education sessions	Number of sessions	Total of community attendees	Venue(s)
Ridgeville, SC	2	2	25	Community Center
Georgetown, SC	8	25	702	Church Ministries Family Reunion Health Fair Professional Clubs
Charleston, SC	8	13	225	Professional Associations School System Staff Meetings

Educational Community Sessions Following the Cancer Education Intervention (continued)

Site	Number of facilitators who performed community education sessions	Number of sessions	Total of community attendees	Venue(s)
Greenville, SC	10	45	1,812	>Centers >Church >Health Fairs >Support Group
Orangeburg, SC (1)	1	1	15	>Staff Meeting
Columbia	2	2	44	>Church
Orangeburg, SC (2)	0	0	0	N/A

Educational Community Sessions Following the Cancer Education Intervention (continued)

Site	Number of facilitators who performed community education sessions	Number of sessions	Total of community attendees	Venue(s)
Johns Island, SC	9	16	469	>Church >Headstart Counselors >Health Program >Home
Denmark, SC	**	**	**	**
Florence, SC	**	**	**	**
TOTAL	40	104	3,292	

** Training sessions were conducted too recently to be evaluated

Strengths of the Study

- Study sample included statewide representation
- Community-based recruitment strategy

Conclusions

- Providing cancer clinical trials information to racial and ethnic minorities led to more positive perceptions of cancer clinical trials
- Future research studies could incorporate a longer follow-up period to assess the behavioral impact of the intervention and whether short-term gains are sustained over time

Future Directions

Future studies could:

- Ascertain the long-term impact of the intervention on perceptions of clinical trials
- Future studies could link the intervention to clinical trial enrollment and to assessments of doctor-patient communication
- Investigators could also assess the extent to which the education programs impact the communication dynamics between patients and their health care providers

Acknowledgements

Funding Sources and Partners:



APPENDIX F

Student Fellows' and Program Director and Associate Directors Posters Given During the IMPaCT Conference

NOV-002 Induces S- Glutathionylation of Serpins A1 and A3 in Human Plasma

Jonathan L. Brown¹, Christina Grek, PhD², Kenneth D. Tew PhD², Danyelle M. Townsend, PhD²

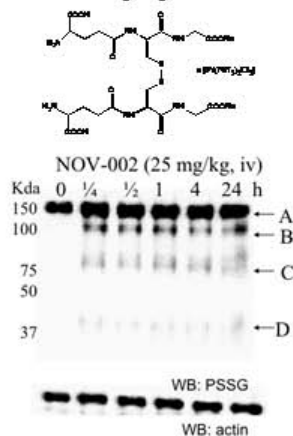
Departments of Biomedical and Pharmaceutical Sciences², Cell and Molecular Pharmacology and Experimental Therapeutics³,
Medical University of South Carolina, Hollings Cancer Center
86 Jonathan Lucas Street, Charleston, SC 29425

ABSTRACT

Serine protease inhibitors (serpins) make up about 2% of the total protein in human serum. Serpins play a role in bone marrow proliferation and are redox regulated. NOV-002 is a glutathione mimetic in Phase II breast cancer trials. NOV-002 treatment leads to bone marrow proliferation through redox modulation. Prior studies using mass spectrometry showed that Serpin A1 and A3 are S-glutathionylated in mouse plasma following NOV-002 treatment. S-glutathionylation is the specific post-translational modification on cysteine residues by the addition of glutathione. S-glutathionylation alters the functionality and / or sub-cellular localization of proteins following oxidative or nitrosative stress. We hypothesize that NOV-002 mediates bone marrow proliferation through S-glutathionylation of Serpin A1 and A3. In the present study, we evaluated whether Serpin A1 and / or A3 were S-glutathionylated in human plasma. Data show that NOV-002 induced S-glutathionylation of Serpin A1 or A3 may mediate myeloproliferative effects of the drug.

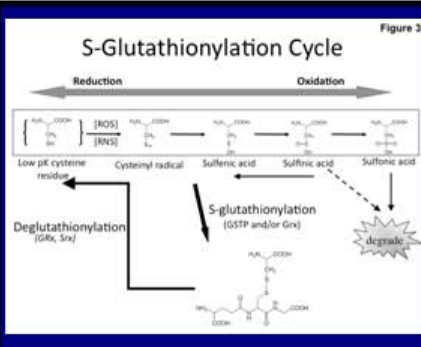
BACKGROUND

NOV-002 induces S-glutathionylation of Serpin A1 and A3 in vivo. Mice were treated with 25 mg/kg, iv. Plasma was collected and analyzed for protein S-glutathionylation. Mass spectrometry identification of S-glutathionylated proteins showed that Serpin A1 (D) and A3 (B) are modified following drug treatment.

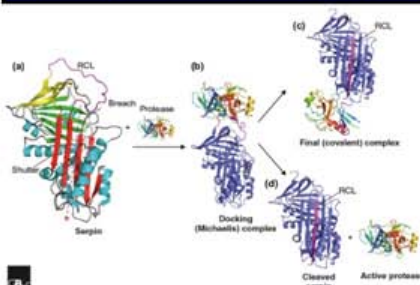


HYPOTHESIS

S-Glutathionylation of Serpin mediates bone marrow proliferation.



Activation of Serpin A1 via S- Glutathionylation



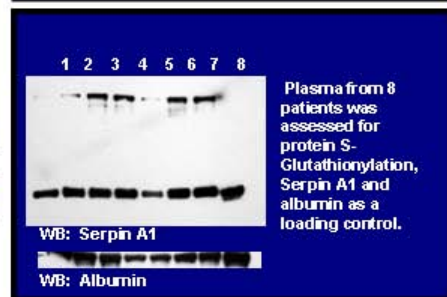
FUNDING SOURCE

Grant Number: Department of Defense W81XWH-09-1-0157, Collaborative Undergraduate HBCU Student Summer Prostate Cancer Training Program.

METHODS

Plasma from 8 patients was collected and stored at -80 °C. Protein concentrations were determined using the Bradford Assay. For *ex vivo* studies 40 ug plasma was treated with 0 – 250 uM NOV-002 for 0- 240 minutes. Proteins were separated under non-reducing conditions by polyacrylamide gel electrophoresis and transferred to nitrocellulose membranes. S-Glutathionylation antibodies (Virogen) were used to evaluate dose- and time- dependent modifications following NOV-002 treatment. The membranes were stripped and probed with Serpin A1 or A3 antibodies. Data are represented as the ratio of modified to native Serpin.

RESULTS



CONCLUSIONS

- NOV-002 oxidative signaling results in S glutathionylation of Serpins A1 and A3 in mouse (*in vivo*) and human (*in vitro*) plasma.
- Serpin iS-glutathionylation could serve as a pharmacodynamic biomarker for NOV-002 bioactivity.
- Since glutathionylation is known to inhibit Serpin function, this effect of NOV-002 could contribute to its ability to reverse cyclophosphamide-induced hematological suppression.

What Factors Can Predict the Success of Sacroneuromodulation When Used in Patients with Urinary Retention

S. Clarke, M. McIntyre MD, R. Rames MD, H. Clarke MD PhD



Abstract

Objective We sought to determine if any preoperative factors could help predict better clinical outcomes in the setting of urinary retention.

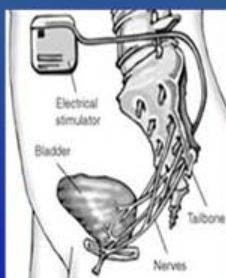
Methods We performed a retrospective chart review of patients who underwent sacroneuromodulation procedures between 2000 and 2010 based on their preoperative, intraoperative and postoperative characteristics. Preoperative characteristics evaluated included age, previous surgeries, neurologic diagnosis, length of retention, invasive and noninvasive urodynamic data. Operative data collected included presence of bellows response, sacral foramen used, number of leads. Postoperative data subjective and objective improvement, progression to IPG implantation, wound infection, complications and need for revision.

Results We identified 54 patients that had undergone 73 sacroneuromodulation lead placements as treatment for urinary retention (17 male, and 35 female). When comparing the procedures that failed to go on to IPG versus those that did we found few differences. The mean age was higher in the failure group 55 vs. 43 years. Mean PVR was also found to be higher in the failure group 613cc versus 570cc. No difference was noted in mean flow rate, max detrusor pressure, or number of stimulating electrodes.

Conclusions The preoperative and intraoperative factors we evaluated do not appear to give us significant prognostic data. Just as we do not fully understand the mechanism of action of this treatment the factors that may portend its success or failure have yet to be fully defined.

Methods

- We performed a retrospective chart review from 2000 to 2010 of procedures performed by three dedicated voiding dysfunction specialist.
- Successful lead placement was defined as going on to IPG implantation
- Results were calculated using simple descriptive statistics to determine if there were preoperative factors that will yield positive outcomes in patients with urinary retention



Results

- We identified 54 patients that had undergone 73 sacroneuromodulation lead placements as treatment for urinary retention

**39 had 1 InterStim procedure
13 had 2 InterStim procedures
3 had 3 InterStim procedures**

- 17 male and 35 female
- Mean age was 50 yrs
- We identified 20 patients that had undergone 26 failed sacroneuromodulation lead placements as treatment for urinary retention

**15 had 1 failed InterStim procedure
5 had 2 failed InterStim procedures**

- We identified 35 patients that had undergone 47 successful sacroneuromodulation lead placements as treatment for urinary retention

**27 had 1 successful InterStim procedure
7 had 2 successful InterStim procedures
1 had 3 successful InterStim procedures**

- Failure: 9 male and 11 female
- Success: 8 male and 27 female
- Mean age was higher in the failure group 55 vs. 43 years
- Mean PVR was also found to be higher in the failure group 613cc versus 570cc
- No difference was noted in mean flow rate, max detrusor pressure, or number of stimulating electrodes or laterality of lead
- Failure was more common in patients that had a higher PVR
- Failure was more common in patient that had shorter operation times

Conclusion

- It appears that shorter surgical times higher volume PVR and older age may predict for failure of SNM when used for urinary retention.
- Prospective studies are needed to confirm this and determine threshold values for these variables

Funding Source

- Grant Number: Department of Defense W81XWH-09-1-0157, Collaborative Undergraduate HBCU Student Summer Prostate Cancer Training Program

DE'ANGELO DINKINS, SC STATE UNIVERSITY



"Redox protein expression and susceptibility to therapeutic intervention in ARCaP prostate cancer cells" De'Angelo Dinkins, Helen Gosnell, Tejas Tirodkar, Marvella E. Ford, Ph.D., Christina Voekel-Johnson, Ph.D.

Medical University of South Carolina, Hollings Cancer Center
86 Jonathan Lucas Street, Charleston, South Carolina, 29425



ABSTRACT

Introduction

Thioredoxin is a redox-regulating protein that plays a central role in regulating cellular redox and preventing cell death. There is a high expression of thioredoxin in cancer cells because the tumor environment is usually under either oxidative or hypoxic stress and both stresses are known to be up-regulators of thioredoxin expression. Prostate cancer is the 2nd leading cancer in men after lung cancer. Indolent disease can be treated fairly well and progresses slowly. However, the more aggressive form of prostate cancer spreads though out the body and there are no curative treatments.

Hypothesis

We tested the hypothesis that increased expression of redox proteins is an underlying cause for the aggressive, therapy-resistant prostate cancer phenotype.

Methods

In our project we looked at the expression of redox proteins and susceptibility to chemotherapy in ARCaPe and ARCaPm cells. Using western blot methods and Image J we were able to quantify the expression of thioredoxins. Susceptibility to chemotherapy was tested in a viability assay.

Results

Western blot analysis indicated increased expression of the redox proteins such thioredoxin 1 and thioredoxin 2 in ARCaPm cells when compared to ARCaPe cells. Our results conclusively showed that Taxol killed both cell types, while TRAIL was more effective on ARCaPe cells than in ARCaPm cells. Combination of TRAIL and taxol resulted in synergistic killing of ARCaPe cells.

METHODS

Western Blot

The Western blot was used to detect the expression of redox proteins in the ARCaP sample. It uses gel electrophoresis to separate native or denatured proteins by the length of the polypeptide. The proteins are transferred to a nitrocellulose membrane where they are detected using antibodies specific to the target protein.

NIH Image

This was used to quantify the western blot signals. Blot was taken to an imager and image was converted to jpg. Then we opened NIH (Image J) we drew boxes around all of the lanes 1 box per lane. Then we analyzed the gels which made plots of the bands. Then we sectioned off each peak and quantified the results. The results were in turn pasted into excel where we generated graphs of our results.

MTS Assay

Cells were plated overnight in triplicates with 96-well plate and treated as indicated the next day. Viability was determined 48 hours after treatment by adding 20ul of Cell Titer 96 Aqueous One Solution (Promega, Cat.#: G3552). Cytotoxicity was calculated following manufacturers instructions.

RESULTS

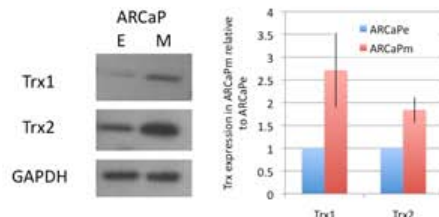


Figure 1. Thioredoxin expression in prostate cancer cell lines

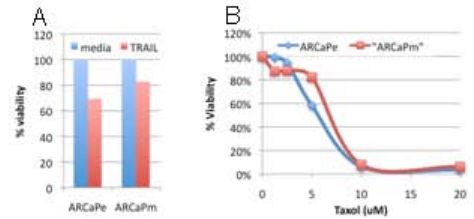


Figure 2. Sensitivity of prostate cancer cell lines to TRAIL (A) and taxol (B)

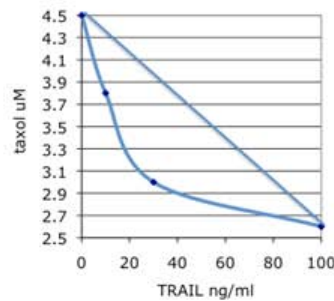


Figure 3. Synergy between taxol and TRAIL in ARCaPe cells

Increased expression of redox protein in ARCaP cells

We used western blot and compared ARCaPe cells next to ARCaPm cells. After the blots were quantified using Image J we could see an increase expression of our redox proteins in the ARCaPm cells. This confirms that redox proteins are more prevalent in the more aggressive prostate cancer phenotype.

Effects of Taxol and TRAIL on cancer cells independently

To investigate the possible effect of Taxol a chemotherapy drug on prostate cancer cells. We did a MTS assay and plated ARCaPe and ARCaPm cells on a 96 well plate and cells were treated with increasing concentrations of Taxol and Depsipeptide. Plates were let in incubator for 48 hr. The colorimetric readings show that Taxol was effective on both ARCaPe and ARCaPm cells but in very high concentrations. Neither cell line was highly sensitive to TRAIL but ARCaPe cells were more sensitive than ARCaPm cells.

Effects of Taxol and TRAIL on cancer cells in combination

Next we investigated the effect of combined treatment with taxol and TRAIL. Viability was determined as described above. Our results indicate that drug synergy was obtained in both ARCaPe cells. ARCaPm cells will be evaluated for synergy in the near future.

CONCLUSIONS

• Combination of taxol and TRAIL may be a novel treatment strategy for advanced prostate cancer.

FUNDING SOURCE

Grant Number: Department of Defense W81XWH-09-1-0157, Collaborative Undergraduate HBCU Student Summer Prostate Cancer Training Program.

EBONIE FULLER, SC STATE UNIVERSITY



Evaluating an Intervention to Improve Perceptions of Cancer Clinical Trials among Racially Diverse Communities in South Carolina

Ebonie Fuller, Elizabeth Garrett-Mayer, Ph.D., Amy Wahlquist, M.S., Melanie S. Jefferson, M.P.H., Rashell Blake, June Streets, Erica Johnson, Heidi Varner, Shannon Johnson, M.P.H., David P. Turner, Ph.D., Marvella E. Ford, Ph.D.,

Medical University of South Carolina, Hollings Cancer Center
85 Jonathan Lucas Street, Charleston, SC 29425



ABSTRACT

Objectives: We conducted a community-based cancer clinical trial education intervention in South Carolina (SC), which has high rates of cancer disparities. However, African Americans are less likely than other groups to participate in clinical trials. Low participation rates appear to be an outcome of negative trial perceptions. **Methods:** We conducted the intervention at 10 sites in eight counties. The intervention consisted of a 30-minute cancer clinical trial educational presentation. It was a component of a larger 4-hour cancer education program. Pre- and post-intervention surveys were administered. The 7-item Followfield instrument was used to assess perceptions of cancer clinical trials. Fisher's exact tests were used to compare the proportion of participants who changed their responses from pre-test to post-test. **Results:** Most of the 195 participants were African American (75.4%) and about half (53.3%) were female. For each Followfield item, a highly statistically significant shift was seen toward more positive perceptions of cancer clinical trials following the intervention ($P < 0.001$). **Conclusion:** The intervention positively influenced trial perceptions. Future studies could evaluate the behavioral impact of the intervention and assess whether short-term gains are sustained.

STATEMENT OF THE PROBLEM

- South Carolina (SC) ranks among the top 20 states in the U.S. with the highest number of cancer deaths
- African Americans in SC have significantly higher cancer mortality rates than European Americans
- Despite higher incidence among African Americans, they are not well represented in cancer clinical trials
- Negative perceptions of cancer clinical trials based on lack of knowledge can negatively impact recruitment in minority populations

METHODS

Study Sample

- Community residents of eight different counties in SC were invited to participate in the study (Figure 1)
- The counties were chosen due to high racial disparities in cancer mortality
- Participant Recruitment
- Participants were recruited primarily by community partners in each locale
- Each locale had a site-specific "Champion" responsible for recruitment
- Institutional Review Board Approval
- The MUSC IRB approved the study protocol

Intervention

- A 30-minute interactive presentation on cancer clinical trials developed by the National Institutes of Health (NIH)/National Cancer Institute (NCI)
- Oral modifications to the NIH/NCI presentation included:
 - Stories of African Americans and cancer mortality data specific to SC
 - Information about the Hollings Cancer Center
- The intervention was part of a larger 3.5-hour education program aimed at increasing general cancer knowledge and prostate cancer knowledge
- Pre- and post-intervention surveys were administered immediately before and after the intervention was delivered at each site

Measures

- Perceptions of cancer clinical trials were assessed by the 7-item Followfield instrument (Followfield et al., 1998)
- Six additional items assessed sociodemographic characteristics
- Statistical Methods
- Survey data were double-entered with SPSS 16.0, SAS 9.1.3, and R 2.6.1.
- Chi-Square tests were used to compare data across sites
- Fisher's Exact tests were used to compare the proportion of who answered yes at the pre-survey and changed their answer to "I don't know" (DK) at the post-survey to the proportion of patients who answered "No/DK" at the pre-survey and changed their answer to yes at the post-survey.

Figure 1. Education Cancer Clinical Trials Intervention Sites



Table 1. Summary of Demographic Characteristics of Participants at Pre-test (N=195)

VARIABLE	N	(%)
Age*		
Less than 50 years	78	(40.0%)
51-64 years	73	(37.4%)
65-75 years	34	(17.4%)
More than 76 years	5	(2.6%)
Hispanic*		
Yes	3	(1.5%)
No	188	(96.4%)
Race*		
African American or Black	147	(75.4%)
American Indian or Alaskan Native	15	(7.7%)
Caucasian or White	28	(14.4%)
Other	0	(0.0%)
Education*		
Less than 8 years	4	(2.1%)
8-11 years	8	(4.1%)
12 years or completed high school	20	(10.3%)
Post high school training other than college	12	(6.2%)
Some college	41	(21.0%)
College graduate	53	(27.2%)
Postgraduate	53	(27.2%)
Marital Status*		
Married or living as married	88	(45.1%)
Widowed	19	(9.7%)
Divorced	24	(12.3%)
Separated	5	(2.6%)
Never married	54	(27.7%)
Household Income*		
\$0-\$19,999	47	(24.1%)
\$20,000-\$39,999	42	(21.5%)
\$40,000-\$59,999	41	(21.0%)
\$60,000-\$79,999	26	(13.3%)
\$80,000+	26	(13.3%)
Gender*		
Male	26	(14.4%)
Female	104	(53.3%)

* Missing data on this variable

FUNDING SOURCE

Grant Number: Department of Defense W81XWH-09-1-0157, Collaborative Undergraduate HBCU Students Summer Prostate Cancer Training Program.

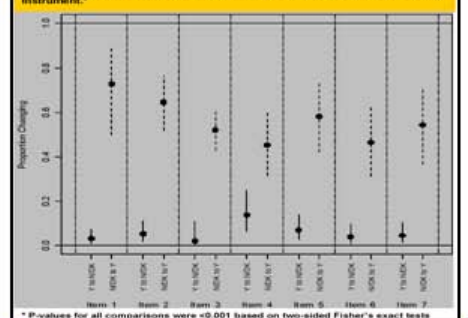
RESULTS

Table 2. Followfield Instrument Items*

- Do you think that patients should be asked to take part in medical research?
- Suppose that you were asked to take part in a research study comparing two treatments, both of which were suitable for your illness. Would you be prepared to take part in a study comparing different treatments?
- Usually the only scientific way to compare one treatment with another is for the choice between the two to be made randomly, rather like tossing a coin. Would you be prepared to take part in a study where treatment was chosen at random?
- If you answered "No" or "Do not know" to Question 3, we would now like to ask you a bit more about this. In a randomized study a choice would be made between two treatments, either of which would be suitable for you. Your doctor and experts in the field do not know for sure if one treatment is better than the other, or if they are both the same, that's why they want to do the study. Would knowing that encourage you to take part?
- In a random choice study, if the treatment you were receiving did not suit you for any reason you could leave the study. Your doctor would then give you whatever other treatment might be appropriate for you. Would that encourage you to take part?
- Before you agreed to enter a random choice study the doctor would tell you all about the two treatments being compared, before you were allocated to one or the other. Would that encourage you to take part?
- If you knew all the following things were taken in account, would you change your mind and agree to take part in the study?
 - Both treatments were completely suitable
 - You could leave the study if the treatment did not suit you
 - There is plenty of information before the random choice was made

* Responses to each item are Yes, No, and Do Not Know

Figure 2. Comparison of Proportion of Respondents Who Changed Perception From Yes to No/DK Versus No/DK to Yes for the Seven Items in the Followfield Instrument.*



* P-values for all comparisons were <0.001 based on two-sided Fisher's exact tests

CONCLUSIONS

- Providing cancer clinical trial information to racial and ethnic minorities led to more positive perceptions of trials.
- The majority of the participants who had less favorable perceptions of cancer clinical trials at pre-test changed their perceptions to more positive perceptions.
- Future interventions could incorporate a longer follow-up period to assess the long-term behavioral impact of the intervention.

Reference: Followfield LJ, Jenkins V, Ehnman C, Sawtell M, Moynihan C, Souhami RL. Attitudes of patients to randomized clinical trials of cancer therapy. Eur J Cancer 1998;34(10):1554-9



Enhancing Adenoviral Gene Delivery to Prostate Cancer Cells

Andrea Gibson, Sutapa Barua, Kaushal Rege and Christina Voelkel-Johnson

Department of Microbiology and Immunology
Medical University of South Carolina, Hollings Cancer Center
86 Jonathan Lucas Street, Charleston, South Carolina 29425



ABSTRACT

Objective

Adenoviral delivery to cancerous cells has potential as a new therapy but is also problematic. One problem is that cancer cells decrease the expression of coxsackie and adenovirus receptor (CAR) which serves as the transduction factor for an adenovirus to enter a cell. Histone deacetylase inhibitors (HDAC) and polymers have been shown to enhance the transduction of adenovirus. In this study we tested the hypothesis that HDACI or the polymer EGDE-3,3' increase adenoviral infection in PC3 prostate cancer cells.

Methods: Infectivity and transgene expression was measured by flow cytometry following exposure to an adenovirus that expresses green fluorescent protein. The percentage of cells that were GFP positive as well as the GFP intensity were calculated.

Results: The results indicate that HDACI increased infectivity in the prostate cancer cells more than 5-fold at MOIs below 10. However EGDE-3,3' did not increase infectivity. Therefore, EGDE-3,3' did not work as well as it did in a previous study using bladder cancer cells.

Conclusions: HDACI may be more suitable for enhancing adenoviral transgene expression in prostate cancer cells.

METHODS

For adenoviral transduction, cells were plated overnight at 2×10^5 cells/well in a 12-well plate. The following day, AdGFP was diluted in medium to the appropriate multiplicity of infection. Cells were then treated with AdGFP in the absence or presence of HDACI. For the experiments with polymers (stock 10mg/ml), virus was diluted to the appropriate MOI and pre-incubated with polymer for 10 minutes at room temperature. After the 10-minute incubation, 100 μ l of media was added to the tube and the medium in each well was replaced with polymer/virus mixture. Cells were assayed for GFP expression and cell death 48-hours post-infection.

All cells were included in the analysis for flow cytometry. PBS was added to the tube consisting of the spent media. After the cells were detached from the wells by the trypsin, they were pooled with the non-adherent cells. Cells were pelleted at 1000 rpm for 10 minutes and pellets resuspended by PBS. 350 μ l of 10% formalin was placed in each sample to fix the cells. Samples were analyzed by the MUSC flow cytometry core facility using a FACSCalibur.

RESULTS

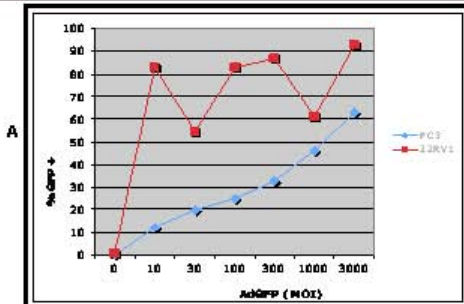


Figure 1 A. Adenoviral infectivity; PC3 cells are more resistant to adenoviral infection than 22RV1 cells.

RESULTS

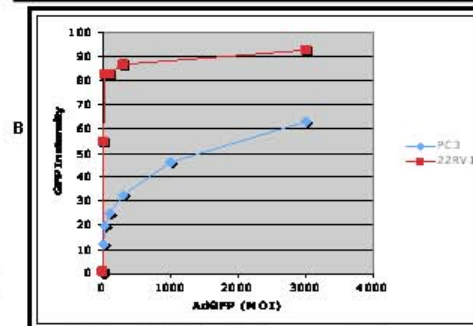


Figure 1 B. Adenoviral infectivity; PC3 cells are more resistant to adenoviral infection than 22RV1 cells.

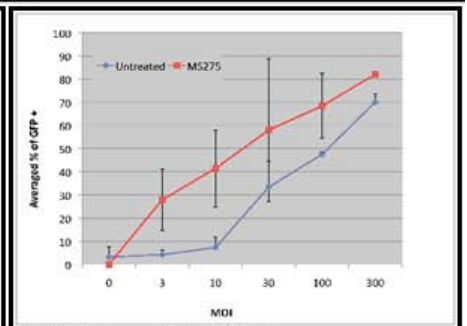


Figure 2. PC3 cells were plated overnight and treated with a virus-drug mixture.

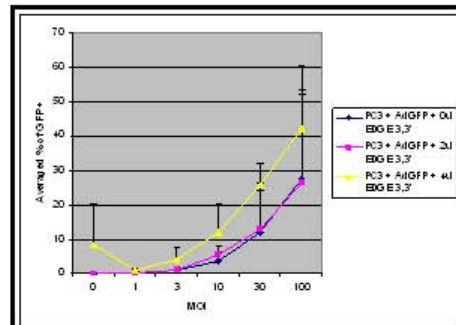


Figure 3. PC3 cells were plated overnight and were treated with a virus-polymer mixture. As a result, it was noticed that polymers did not enhance the infectivity of cells with AdGFP.

DISCUSSION

PC3 treated with AdGFP + HDACI

- Results showed that MS-275 enhanced infectivity in PC3 cells, which is similar to previous study with LNCaP cells (Kamran et al. Cancer Gene Therapy 14:327 (2007)).

PC3 treated with AdGFP + Polymer

- Results showed that the polymer did not increase infectivity at 2x/well.

This study is similar to a previous one used the same polymer EGDE-3,3' in bladder cancer cells, which showed that the polymer EGDE-3,3' can enhance transduction of adenovirus in cells that lack CAR expression (Kamran et al. Molecular Pharmacology 6: 1612, 2009). However, this experiment showed that EGDE-3,3' polymer did not enhance adenoviral transduction in PC3 cells. Results with 4 μ l polymer/well suggested that higher concentrations may be required for adenoviral transduction of prostate cancer cells.

CONCLUSIONS

- EGDE-3,3' with AdGFP did not enhance infectivity in PC3 cells at concentrations that were previously found effective in bladder cancer cells.
- A notable increase of infectivity in the cells that were treated with AdGFP and MS275.

FUNDING SOURCE

Grant Number: Department of Defense W81XWH-09-1-0157, Collaborative Undergraduate HBCU Students Summer Prostate Cancer Training Program.

CODANIELLE GREEN, SC STATE UNIVERSITY



Role of ABCA2 in Prostate Tumor Progression
 CoDanielle Green¹, Jody Mack², Ph.D., Danyelle M. Townsend², Ph.D., Kenneth D. Tew², Ph.D. D. Sc.,
 Departments of Biomedical and Pharmaceutical Sciences²; Cell and Molecular Pharmacology and Experimental Therapeutics²
 Medical University of South Carolina, Hollings Cancer Center, 86 Jonathan Lucas Street, Charleston, SC, 29425



ABSTRACT

BACKGROUND: Prostate cancer is responsible for an estimated 33% of all newly diagnosed cancer in men. Unfortunately, the tumor caused by the disease do not always respond to the drug (chemotherapy). Therefore, determining what causes the tumor to become resistant is important to efficiently treat the cancer. This study involves determining the role of ABCA2 expression because it has been associated with resistance to chemotherapy and multi-drug.

OBJECTIVES: The objectives were to determine if ABCA2 is correlated with tumor progression and to determine whether ABCA2 has an effect on the grade of prostate tumor and incidence of metastasis.

METHODS: To examine the objectives, an ABCA2 knock-out line was created using the Transposon Activation of Mouse Prostate (TRAMP) model and compared to wild type by various methods including: Western Blotting Analysis, PCR, MRI imaging, Vimentin and Desmin Analysis, Scratch Assays, and Transwell Assays.

RESULTS: Although prostate tumor progression was similar in both lines, the incidence of metastasis was elevated in the knock-out.

CONCLUSION: This study increases our understanding of the role of a protein which could indeed be the link to moving treatments so that they will overcome the occurrence of multi drug resistance and tumor relapse.

RESULTS

Fig 1. ABCA2 expression is elevated in TRAMP prostatic epithelia compared to WT. Immunohistochemical analysis of dorsal prostate at 20 weeks of age reveal a significant elevation in ABCA2 expression in TRAMP prostate compared to that of WT. Average immunoscore for relative ABCA2 expression in WT dorsal prostate is significantly lower than WT/Tg ($P < 0.0001$). HEI/Tg ($P = 0.008$), but not of KO/Tg ($P = 0.16$). The KO and KO/Tg sample correct for background staining of the anti-ABCA2 rabbit polyclonal antibody. Images were taken at 10x magnification. Scale bar represents 100 μ m.

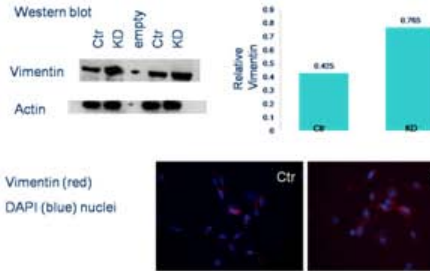
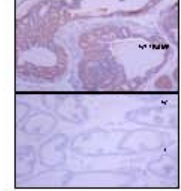
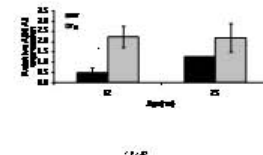


Fig 3 Vimentin Expression is elevated in KD. Tissues were fixed in plastic form cassettes and fixed overnight in 4% paraformaldehyde/PBS pH 7.4 and processed at the Histology Core facility (MUSC Dept of Pathology & Laboratory Medicine). Paraffin sections were deparaffinized and hybridized using Anti-Vimentin (Vector Scientific) followed by anti-DAPI (Vector Scientific). After washing twice in dH₂O, antigen retrieval was carried out using a steamer bath in 10 mM sodium citrate pH 6.0 for 30 min. Endogenous peroxidase activity was blocked by a 10 min incubation in 3% H₂O₂/bovine serum albumin. Sections were then blocked in 10% goat horse serum (for rabbit or mouse primary antibodies, respectively) containing 0.1% Triton X-100 and 1% bovine serum albumin in phosphate buffered saline (PBS) pH 7.4. Sections were incubated in primary antibody diluted in blocking agent overnight at 4 °C at the following dilutions: ABCA2, 1:500; 8-OHAG (Abcam), 1:300; 4HNE (Calbiochem), 1:100; vimentin (Santa Cruz), 1:150; desmin (Abcam), 1:200; PCNA (Abcam), 1:400. Slides were developed using the rabbit or mouse Universal ABC kit (Calbiochem) per the manufacturer's instructions, counterstained in 10% hematoxylin/dH₂O (Vector Scientific) and analyzed by light microscopy.

CONCLUSIONS

- In Mice,
 - ABCA2 expression in dorsal prostate is elevated in TRAMP compared to WT mice; expression increases over time.
 - Prostate tumor progression is similar, but incidence of metastatic tumor is elevated.
- In D6P2T cells,
 - ABCA2 knock-down significantly inhibits chemotaxis in a transwell assay.
 - However, expression of vimentin (marker of EMT) in KD is elevated.

FUNDING SOURCE

Grant Number: Department of Defense W81XWH-09-1-0157, Collaborative Undergraduate HBCU Student Summer Prostate Cancer Training Program.

ABCA2 transporter deficiency reduces incidence of TRAMP prostate tumor metastasis and cellular chemotactic migration.

Mack JI, Halle KL, Green C, Townsend DM, and Tew KD. Cancer Letters. 2011. Jan;283(2):134-141.

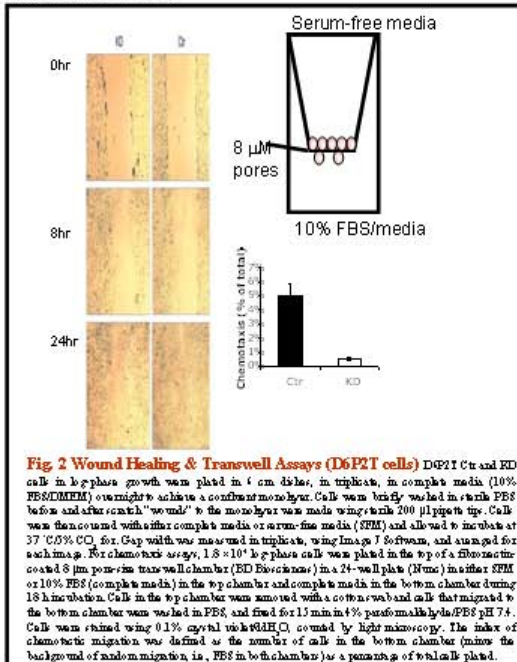
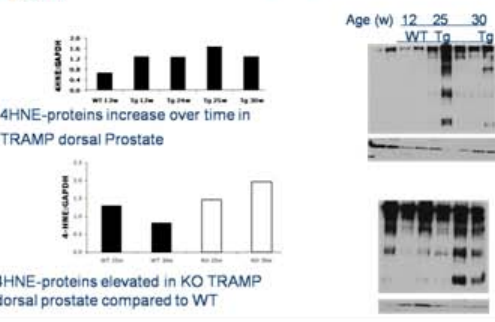


Fig 4 Elevated ROS/RNS-induced 4-hydroxynonenal modified proteins



PROGRAM DIRECTOR AND ASSOCIATE DIRECTORS

Marvella E. Ford, PhD (Medical University of South Carolina)

Rebecca Bullard-Dillard, PhD (Claflin University)

Judith D. Salley, PhD (SC State University)

Leroy Davis, PhD (Voorhees College)



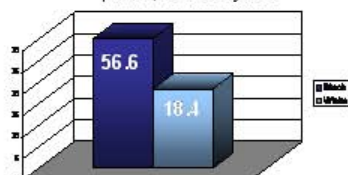
Innovative Minds in Prostate Cancer Today Collaborative Undergraduate HBCU Student Summer Prostate Cancer Training Program

DIRECTORS: Marvella E. Ford, Ph.D. (Medical University of South Carolina)
Rebecca Bullard-Dillard, Ph.D. (Claflin University)
Judith D. Salley, Ph.D. (SC State University)
Leroy Davis, Ph.D. (Voorhees College)

PROSTATE CANCER DISPARITIES IN SOUTH CAROLINA

Prostate cancer is the second most common cause of cancer death among men in the U.S. and is a major public health problem. South Carolina (SC) ranks 3rd in the nation in prostate cancer deaths.

2007 Prostate Cancer Age-Adjusted Mortality Rates per 100,000 in SC by Race



South Carolina Department of Health and Environmental Control: Age Adjusted Rates: 2000 US Standard Population

OVERARCHING GOAL AND SPECIFIC AIMS

There is a critical need to increase the number of racially and ethnically diverse prostate cancer researchers.

GOAL

The goal of the Training Program is to recruit the next generation of prostate cancer researchers by exposing undergraduate students ("Student Fellows") from Claflin University (CU), South Carolina State University (SCSU), and Voorhees College (VC) to prostate cancer research at the Medical University of South Carolina (MUSC), and training them to meaningfully participate in local research activities.

SPECIFIC AIMS

- 1) To provide training in the basics of research design and methods to 4 Student Fellows each year through participation in the MUSC Summer Undergraduate Research Program
- 2) To immerse 4 Student Fellows each year in a prostate cancer research training curriculum.

MUSC SUMMER UNDERGRADUATE RESEARCH TRAINING PROGRAM (SURP)

- A 10-week program to identify and recruit the state's leading students to enroll in graduate programs at MUSC.
- Student Fellows are given an overview of the many research areas available for study in Biomedical Research.
- Student Fellows receive 15 hours of academic credit for participation.
- Student Fellows work with an MUSC research mentor to conduct the prostate cancer research project.
- At completion, each Student Fellow will prepare a research paper and give an oral presentation describing his or her research project results.

PROSTATE CANCER TRAINING PROGRAM STRUCTURE



PROSTATE CANCER RESEARCH TRAINING CURRICULUM		
Week	Topic	Instructor
Week 1	Welcome and Overview	Marvella E. Ford, Ph.D. Melanie S. Jefferson, MPH
Week 1 Basic Science Research Lecture	Overview of the Hollings Cancer Center	Andrew S. Kraft, M.D.
Week 2	Introduction to Health Disparities Research	Rebecca Bullard-Dillard, Ph.D., CU Judith Salley, Ph.D., SCSU Leroy Davis, Ph.D., VC
Week 3 Clinical Research Lecture	Anatomy and the Function of the Prostate	Harry S. Clarke, M.D.
Week 3 Population Science Research Lecture	Vitamin D and Prostate Cancer	Sebastiano Gattoni-Celi, M.D.
Week 3 Clinical Research Lecture	Two Part Roundtable Discussion: • Pursuing a Graduate Dual Degree • Completing a Residency in Radiation Oncology	Gabrielle Cannick, DDS, Ph.D. Leander Cannick, M.D.
Week 4 Basic Science Research Lecture	Apoptosis of Prostate Cancer Cells	Christina Voelkel-Johnson, Ph.D.
Week 4 Biostatistical Methods Lecture	Biostatistical Issues in Prostate Cancer Research	Elizabeth Garrett-Mayer, Ph.D.
Week 5 Population Science Research Lecture	Epidemiologic Issues in Prostate Cancer Research	Anthony Alberg, Ph.D.
Week 5 Population Science Research Lecture	Prostate Cancer Research: Perspectives of Community Members	Debbie Bryant, RN
Week 6 Biostatistical Methods Research Lecture	Statistical Genetics	Emily Kistner-Griffin, Ph.D.
Week 6 Basic Science Research Lecture	Developmental Transcription Factors in Prostate Cancer	Demetri Spyropoulos, Ph.D.
Week 7 Population Science Research Lecture	Qualitative Research Methods	Charlene Pope, Ph.D.
Week 8 Population Science Research Lecture	Lunch and Lecture	Marvella E. Ford, Ph.D.
Week 8 Population Science Research Lecture	Project Sugar: Community-based genetic research project among the Sea Islanders (Gullahs) in South Carolina	Ida J. Spruiell, Ph.D.
Week 9 Tips for Preparing Graduate School Applications	Improving Graduate School Admission Rates	Cynthia F. Wright, Ph.D.
Week 9 Rehearsals	Research Presentation Rehearsals and Evaluations	All Research Students
Week 10 Rehearsals and Evaluations	Research Presentation Rehearsals and Evaluations	All Research Students

FUNDING SOURCE

- Grant Number: Department of Defense W81XWH-09-1-0157, Collaborative Undergraduate HBCU Student Summer Prostate Cancer Training Program.

STUDENT FELLOW RESEARCH ACCOMPLISHMENTS

Student Fellow Summer Prostate Cancer Training Program Mentors And Research Topics			
2009			
Student Name	Academic Institution	MUSC Research Mentor	Research Topic
Scharan Clarke	Claflin University	Harry S. Clarke, M.D.	Does the Preoperative Evaluation of Men with Bladder Obstruction Affect the Outcomes of Outlet Reduction Procedures?
Andrea Gibson	Claflin University	Christina Voelkel-Johnson, Ph.D.	Enhancing Gene Delivery To Cancer Cells
Co-Danielle Green	SC State University	Danyelle Townsend, Ph.D.	Role of ABCA2 in Prostate Tumor Progression
Samantha Jones	SC State University	Shikhar Mehrotra, Ph.D. and Mike Nishimura, Ph.D.	Isolation and Ex Vivo Expansion of Antigen-Specific CD8+ T cells
2010			
Jonathan Brown	Claflin University	Danyelle Townsend, Ph.D.	NOV-002 Induces S-Glutathionylation of Serpin A1 and A3 in Human Plasma
Scharan Clarke	Claflin University	Harry Clarke, Ph.D.	What Factors Can Predict the Success of Sacro neuromodulation When Used in Patients with Urinary Retention
DeAngelo Dinkins	SC State University	Christina Voelkel-Johnson, Ph.D.	Redox protein expression and susceptibility to therapeutic intervention in ARCA prostate cancer cells
Ebonie Fuller	SC State University	Marvella E. Ford, Ph.D.	Evaluating an Intervention to Improve Perceptions of Cancer Clinical Trials among Racially Diverse Communities in South Carolina

2009-2010 STUDENT FELLOWS



FUTURE DIRECTIONS

- Initiate a Student Fellow Alumni Program to effectively track the progress of past Student Fellows and update them on current prostate cancer research findings
- Incorporate a field experience component into the Prostate Cancer Training Curriculum to allow them to interact with community members with/at risk for prostate cancer
- Submit a new application to the DOD CDMP to continue funding

APPENDIX G
SCIENTIFIC ACCOMPLISHMENTS OF THE STUDENT FELLOWS TO DATE

NOTE: The Students' Accomplishments Table includes 2009-2010 Student Fellows

Student Name	Institution	DOD/RBC Student Fellow	Summer Research	Publications	Presentations	GRE Test Status	Graduate School Admission
Scharan Clarke	Claflin University	2009 DOD	2009: Does the Preoperative Evaluation of Men with Bladder Obstruction Affect the Outcomes of Outlet Reduction Procedures?		2009 MUSC Summer Undergraduate Research Program	Plans to take the GRE in February 2011	Plans to apply to the following institutions: 1.) University of South Carolina, School of Public Health 2.) The Medical College of Georgia
Andrea Gibson	Claflin University	2009 DOD	Enhancing Gene Delivery To Cancer Cells		2009 MUSC Summer Undergraduate Research Program Poster Presentation at the 2011 IMPaCT Conference	Plans to take the GRE on February 25, 2011.	Plans to apply to a graduate school program.
Co-Danielle Green	SC State University	2009 DOD	Role of ABCA2 in Prostate Tumor Progression	Mack JT, et.al. ABCA2 transporter deficiency reduces incidence of TRAMP prostate tumor metastasis and cellular chemotactic migration. Cancer Letters. 2011. Jan 28; 300(2): 154 -161.	2009 MUSC Summer Undergraduate Research Program Poster Presentation at the 2011 IMPaCT Conference	Plans to take the GRE in the summer of 2011.	Plans to apply to the following institutions: 1.) Medical University of South Carolina 2.) Mercer 3.) University of South Carolina
Samantha Jones	SC State University	2009 DOD	Isolation and <i>ex vivo</i> expansion of antigen-specific CD8 ⁺ T cells		2009 MUSC Summer Undergraduate Research Program		

Student Name	Institution	DOD/RBC Student Fellow	Summer Research	Publications	Presentations	GRE Test Status	Graduate School Admission
Jonathan Brown	Claflin University	2010 DOD	NOV-002 Induces S-Glutathionylation of Serpin A1 and A3 in Human Plasma		2010 MUSC Summer Undergraduate Research Program Poster Presentation at the 2011 IMPaCT Conference	Plans to take the GRE: Date Unknown	Plans to apply to a graduate school program.
Scharan Clarke	Claflin University	2010 DOD	2010: What Factors Can Predict the Success of Sacroneuromodulation When Used in Patients with Urinary Retention		2010 MUSC Summer Undergraduate Research Program Poster Presentation at the 2011 IMPaCT Conference	Plans to take the GRE in February 2011	Plans to apply to the following institutions: 1.) University of South Carolina, School of Public Health 2.) The Medical College of Georgia
DeAngelo Dinkins	SC State University	2010 DOD	"Redox protein expression and susceptibility to therapeutic intervention in ARCaP prostate cancer cells"		2010 MUSC Summer Undergraduate Research Program Poster Presentation at the 2011 IMPaCT Conference	Plans to take the GRE: Date Unknown	Plans to apply to the following Institutions: 1.) Medical University of South Carolina 2.) Vanderbilt 3.) University of North Carolina-Chapel Hill
Ebonie Fuller	SC State University	2010 DOD	Evaluating an Intervention to Improve Perceptions of Cancer Clinical Trials among Racially Diverse Communities in South Carolina	Manuscript entitled "Evaluating an Intervention to Improve Clinical Trial Perceptions among Racially Diverse Communities in South Carolina" is in preparation to be submitted to the American Journal of Public Health.	2010 MUSC Summer Undergraduate Research Program 2010 MUSC Student Research Day Oral presentation at the 2010 MUSC Student Research Day Poster Presentation at the 2011 IMPaCT Conference	Plans to take the MCAT Medical School Exam	Plans to apply to the following institutions: 1.) Medical University of South Carolina 2.) East Carolina University