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TITLE: Epidermal Growth Factor (EGF) Receptor Intron 1 CA Repeat Polymorphisms in African-American and Caucasian Males: Influence on Prostate Cancer Risk or Disease Progression and Interaction with Androgen Receptor CAG Repeat Polymorphisms

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13. ABSTRACT (Maximum 200 Words) We are investigating the effect of polymorphic epidermal growth factor receptor (EGFR) gene intron 1 CA repeat on prostate cancer (CaP) development, alone or in combination with a known androgen receptor gene CAG repeat polymorphism. We will determine the lengths of these repeats in DNA from African-American and Caucasian men with CaP. The data will be analyzed for nay correlation using both parameters with clinical outcome (age of onset, rapid progression, or metastasis). A biostatistician has been recruited to the study and a new statistical analysis plan has been developed. The implementation of the new HIPAA regulations by the Cooper Hospital/University Medical Center Institutional Review Board this year has resulted in additional delays in obtaining documentation required for the revised human subjects protocol. Thus, the Human Subjects Protocol has not yet been approved by the US Army Medical Research and Materiel Command Human Subjects Research Review Board (USAMRMC HSRRB). Since we have not been given approval to initiate the study, there is no data to report. However, the current Human Subjects Protection Scientist at the DOD HSRRB has given verbal assurance that the HIPAA documentation was the last piece need for approval of the protocol, and we anticipate initiating the project very shortly.				
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INTRODUCTION: African-Americans are at increased risk of developing prostate cancer (CaP) relative to whites, and the lengths of two polymorphic repeats in the first exon of the androgen receptor (AR) gene contribute to that risk (Ries *et al*, 1990; Parker *et al*, 1996). The CAG repeat length is best correlated with prostate cancer risk, shorter repeats being associated with higher risk, and the prevalence of the shorter CAG alleles is greatest in African-American men, intermediate in Caucasian, and least in Asian-American men (Faber *et al*, 1989; Irvine *et al*, 1995; Kantoff *et al*, 1998; Pettaway, 1999). However, a multigenic etiology for CaP is likely. A polymorphic CA repeat has been described in intron 1 of the epidermal growth factor receptor (EGFR) gene, and the length of the repeat inversely correlated with transcriptional activity *in vitro* (Chi *et al*, 1992; Gebhardt *et al*, 1999). Preliminary evidence suggests that the CA repeat status affects EGFR content in breast cancer, and that shorter repeats might be a predisposing factor for breast cancer (Buerger *et al*, 2000). The EGFR is also important in regulation of prostatic epithelial and CaP cell growth, and androgen may affect that by increasing the levels of EGFR and its' ligands in CaP cells (Schuurmans *et al*, 1991; Liu *et al*, 1993). Shorter CA repeats in intron 1 of the EGFR gene, by resulting in transcriptional enhancement of EGF receptor expression, and potentially also by affecting alternative splicing of the EGFR transcript, could synergize with shorter CAG androgen receptor AR repeats to increase the risk of early onset prostate cancer and promote the development of androgen-independent, metastatic prostate cancer. In collaboration with The Prostate Cancer Risk Assessment Program at Cooper Hospital/ University Medical Center, we will isolate DNA from blood samples from 300 African-American and Caucasian American men with (and some without) prostate cancer. We will determine the length of these two repeats, to determine whether the EGFR CA repeat, alone or in combination with the AR CAG repeat, affects CaP risk. Lymphoblastoid cell lines will be established for a representative subset of these samples, and will be made available to other researchers at the end of this study. The data will be analyzed for any correlation using both parameters with clinical outcome (age of onset, rapid progression, or metastasis).

BODY: Based on USAMRMC recommendation, a biostatistician was recruited to the study and a new statistical analysis plan was developed. A major restructuring of the Institutional Review Board of Cooper Hospital/ University Medical Center took place during the 2001-2002, and this resulted in a series of required changes in the informed consent form and other delays in obtaining documents required for the revised human subjects protocol. In response to a recent request by my collaborator, Dr. Joel Marmar, the Cooper Hospital/ University Medical Center IRB now considers the present study (funded by award number DAMD17-01-1-0080) to be a sub-study of the Regional Prostate Cancer Registry and Risk Assessment Program at Cooper Hospital/ University Medical Center. Further delays were caused by turnover of HSRRB reviewers. The implementation of the new HIPAA regulations by the Cooper Hospital/ University Medical Center Institutional Review Board this year has resulted in additional delays in obtaining documentation required for the revised human subjects protocol. However, the approved HIPAA documents have recently been submitted to the US Army Medical Research and Materiel Command Human Subjects Research Review Board (USAMRMC HSRRB). Since we have not been given HSRRB approval to initiate the study, there is no data to report. We are therefore requesting a change in the funding period to reflect the time required to obtain all approvals necessary to initiate the proposed research. The HIPAA addendum and revised Human subjects documents are appended.

KEY RESEARCH ACCOMPLISHMENTS: None, since we have not been authorized to initiate the research.

REPORTABLE OUTCOMES: None.

CONCLUSIONS: Despite tremendous progress in research into the origins of prostate cancer (CaP), there are still many important, unresolved questions about the etiology of this common cancer. Perhaps the most urgent problem facing prostate cancer researchers -- and those with the disease -- is to identify the subset of CaP sufferers whose cancer will progress rapidly. Despite extensive research, no single marker has arisen as a definitive marker of such cancers. Indeed, a multigenic etiology for CaP is extremely likely. Among the candidate genes are those encoding the androgen receptor and the epidermal growth factor receptor (EGFR). The EGFR is clearly important in the regulation of prostatic epithelial and CaP cell growth, and is frequently overexpressed in BPH and CaP cells, but no studies have convincingly demonstrated that it is of great use in predicting the course of a particular CaP case. However, a polymorphic CA repeat has been described in intron 1 of the epidermal growth factor receptor (EGFR) gene, and the length of the repeat has recently been inversely correlated with transcriptional activity *in vitro* (Chi *et al*, 1992; Gebhardt *et al*, 1999). Androgen may also influence the expression of the EGFR by increasing the levels of its ligands, and perhaps directly in CaP cells (Schuurmans *et al*, 1991; Liu *et al*, 1993). However, the possible contribution of EGFR CA repeat polymorphisms on prostate cancer risk or progression has never been investigated. Shorter CA repeats in intron 1 of the EGFR gene, by resulting in transcriptional enhancement of EGF receptor expression, and potentially also by affecting alternative splicing of the EGFR transcript, could synergize with shorter CAG androgen receptor AR repeats to increase the risk of early onset prostate cancer and promote the development of androgen-independent, metastatic prostate cancer. This proposal will both begin to address these possibilities, and provide resources for definitive future studies.

We are looking forward with great anticipation to the approval of the revised human subjects research protocol so that we can initiate this research.

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**HSRRB Log No. A-10414/ PC001407 - " Epidermal Growth Factor (EGF) Receptor intron 1
CA repeat polymorphisms in African-American and Caucasian males: Influence on Prostate
Cancer risk or disease progression and interaction with Androgen receptor CAG repeat
polymorphisms."**

Human Subjects Protocol

1. This grant will utilize specimens and information accrued through The Prostate Cancer Risk Assessment Program, a collaborative project of Cooper Hospital/ University Medical Center and The Coriell Institute for Medical Research. The overall study is entitled "Development of a regional prostate cancer registry & risk assessment program".
2. This protocol does NOT involve the testing of Investigational New Drugs or Devices.
3. Principal Investigator (PC001407):

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5. Time required to complete: Expected Start: October 1, 2003
Completion: September 31, 2006

6 - 9. Protocol

- a. Research Hypotheses/ Objectives: This study involves the development of a prostate cancer database that will collect data not currently available on prostate cancer patients and their family members. Personal information and blood samples will be collected from all participants, and tissue samples will be collected from participants that undergo medically indicated biopsies or surgeries. Regarding PC001407, I hypothesize that shorter CA repeats in intron 1 of the EGFR gene, by resulting in transcriptional enhancement of EGF receptor expression, will synergize with shorter CAG androgen receptor AR repeats to increase the risk of early onset prostate cancer and/ or promote the development of androgen-independent, aggressive prostate cancer. The status of Epidermal Growth Factor (EGF) Receptor intron 1 CA repeat and androgen receptor CAG repeat polymorphisms in African-American and Caucasian males will be determined by PCR analysis of DNA isolated from blood samples. These data will be studied in conjunction with the personal and medical information to determine whether the status of the EGF receptor polymorphism, alone or in combination with the androgen receptor polymorphism, influences the age of onset or biological characteristics (e.g., hormone dependence, invasiveness, metastasis) of prostate cancer. Further details are described in the included abstract.
- b. Study Population: The study population will be comprised of approximately 300 males recruited from individuals who come to Cooper Hospital for the treatment of prostate cancer and via the Prostate Cancer Risk Assessment Program at Cooper Hospital. Cooper Hospital serves primarily Camden County and western Burlington County, New Jersey, and ethnically diverse area with significant African-American, Caucasian, and Hispanic populations.
- c. Inclusion and Exclusion Criteria: All subjects recruited will be males in the age range of 35 - 69 years. Carcinoma of the prostate (CaP) is rare among individuals under age 35, whereas prostatic intraepithelial neoplasia (PIN) the presumed precursor of CaP, is very common among men older than 70, so older individuals are less likely to be informative regarding hereditary predisposition. Because the frequency of the various EGF receptor intron 1 CA repeat lengths in African-American men is currently unknown, and since African-American men are at greater risk of prostate cancer than the general population, we will recruit a significant fraction of subjects from the African-American community. Subjects accrued to date under the previously approved Prostate Cancer Risk Assessment Program protocol are ca. 50% African-American and 50% Caucasian.
- d. Informed Consent Process: Clinical nursing staff at Cooper Hospital/University Medical Center will explain The Prostate Cancer Risk Assessment Program in lay terms to prospective subjects who come to the weekly screening clinic ("self-recruitment"). The Prostate Cancer Risk Assessment Program is open to men between the ages of 35 and 69 who are African-American, or of any race with a family history of prostate cancer. Prostate cancer patients of Dr. Joel Marmor will also be offered the opportunity to enroll in the study. Individuals uncertain about participation may discuss the study with friends and family members and return at a later time. Interested individuals will then be talked through the informed consent form (appended), with particular attention being focussed on the clauses regarding (a) the choice to be informed of any clinical implications of their results in the context of this or other relevant prostate cancer studies, (b) the risks of participation in the study, and (c) sample donation. Witnesses may be other clinic personnel or any other individual the subjects choose. As the document is discussed, the subjects and their witnesses will be asked to initial each page to indicate that it has been explained to

them, as well as to sign the last page of the document to indicate their agreement to participate in the study. Two copies of the consent form will be completed so that the subjects can keep an original copy.

e. Sample Size: A target of 300 individuals will be sought over the course of 3 years. (The overall target for the Regional Prostate Cancer Registry and Risk Assessment Program is 400 subjects, but the time and funds for PC001407 will allow for analysis of 300.) By recommendation of peer review, a biostatistician has been consulted regarding sample size (appended), and will be consulted for subsequent data analyses. EGFR intron 1 CA repeat allele frequencies in the general populations of African-American and Caucasian American men will be determined by analysis of DNA samples from apparently normal individuals in existing Coriell Cell Repository panels.

f. Protocol Design: Male subjects (300) will be recruited from individuals who come to Cooper Hospital for the treatment of prostate cancer and via the Prostate Cancer Risk Assessment Program at Cooper Hospital as described in b - d above. Notices will be published as in the appended Cooper Health system newsletter. After informed consent is obtained as described in (d), subjects will be asked to complete a Health History Questionnaire (appended), and to donate 3 (~10 ml each) tubes of blood. One tube will be used by the hospital for medical diagnosis (e.g., Prostate Specific Antigen level), while the other tubes will be used at the Coriell Institute for Medical Research for (a) extraction of DNA and (b) isolation and cryopreservation of lymphocytes. Blood will be collected no more than once per year for the purposes of this study. The lengths of the EGFR intron 1 CA repeat and the AR CAG repeat will be determined by PCR analysis of the DNA (of the samples accrued to date on a previous protocol, the AR repeat has already been analyzed in several dozen). Epstein-Barr virus-immortalized lymphoblastoid cell lines will be established for individuals representing the possible combinations of these two polymorphisms. These cell lines will be deposited in the National Institute of Aging Repository in the Coriell Cell Repositories, and will be available to other researchers at the end of this study. We will also utilize prostate biopsies, when obtained as part of the subjects' medical care, to examine EGFR and AR expression and initiate prostate cell lines. The specimens, health histories, and clinical information will be encoded as PS#### (e.g., PS100, PS101, etc.) by the Cooper Hospital clinical staff, such that all specimens and information received by The Coriell Institute for Medical Research will be separated from subject names. Coriell will receive only coded summaries of the Health History Questionnaires. Any cell lines accepted by the Coriell Cell Repositories for distribution to other researchers will be given new code numbers (e.g., AG00000) to ensure confidentiality. For PS#### cell lines to be submitted to the Coriell Cell Repositories, Dr. Joel Marmar's clinical staff will assign new numbers from a list of the next available AG numbers; the list indicating the PS #s corresponding to the new AG numbers will be kept by his office for 4 years after completion of the study.

g. Risks to Subjects: As this is not an interventional protocol, this project poses no greater than minimal risk to participants. Risks noted in the consent form include the risk of discovering a genetic predisposition to cancer, which may cause concern. Subjects may also have concerns even if they are not in the future told that they have a gene alteration that has been linked to an increased risk of prostate cancer. Subjects do not have to agree to have this information revealed to them or their family members. The risks and discomfort associated with giving blood include the possibility of bleeding and bruising. This rarely causes a significant problem.

h. Benefits to Subjects: As noted in the consent form, subjects will not receive any immediate benefits as a result of participation in this study. It is possible that the study will reveal known or novel genetic polymorphisms that would indicate a statistically greater or lesser prostate cancer risk than the general population. This might prompt an individual to have regular screening for prostate cancer, which could affect their prognosis should cancer be discovered. However, such information is more likely to be of use in the future, rather than to subjects recruited in the current study.

i. Roles and Responsibilities of Study Personnel: Local review boards have not found the protocol to be of greater than minimal risk, so no medical monitor has been assigned.

David K. Moscatello, Ph.D. Role: Principal Investigator (PC001407), 40%. Lymphocyte and DNA isolation, analysis of EGFR intron 1 CA repeats, analysis of Androgen receptor CAG repeats, preparation of DNA, RNA, and protein lysates from prostate specimens, immunohistochemistry and western blotting, reverse transcription-polymerase chain reaction (RT-PCR), Southern and Northern blotting, cryopreservation of viable prostate biopsies, and data analysis.

Bender, Patrick K., Ph.D. (Associate Professor and Supervisor, Division of Molecular Biology, Coriell Institute for Medical Research, 5%. Role: Analysis of Androgen Receptor CAG repeats.

Grana, Generosa, M.D., Assistant Professor of Hematology/ Oncology and Medical Director, The Cancer Risk Evaluation Center, Cooper Hospital/University Medical Center, 5%. Role: Medical Director, The Cancer Risk Evaluation Center.

Marmar, Joel, M.D., Professor of Urology and Head, Division of Urology, Cooper Hospital/ University Medical Center, 5%. Role: Procurement of benign and malignant prostate specimens.

Juliette M May, Cooper Hospital/University Medical Center, 25%. Role: Subject recruitment, interviews, blood collection, data entry and encoding.

Nancey Coker, B.A., Technician, Coriell Institute for Medical Research, 50%. Role: Lymphocyte isolation and cryopreservation, DNA isolation, and PCR.

Constantine Daskalakis, Sc.D., Biostatistics section of the Department of Medicine, Thomas Jefferson University, Philadelphia, PA, 5%. Role: Consultant for study design and data analyses.

10. Reporting of serious and unexpected adverse events. This is not an IND or IDE protocol. No medical interventions are proposed. However, there is a remote possibility of a severe adverse event such as excessive bleeding or infection as a result of blood collection. Should such an event occur, Adverse experiences that are both serious and unexpected will be immediately reported by telephone to the USAMRMC Deputy for Regulatory Compliance and Quality (301-619-2165) and send information by facsimile to 301-619-7803). A written report will follow the initial telephone call within 3 working days.

11. Description of Protocol Drug(s) or Device(s): Not applicable.

12. Disposition of data: All health history and clinical records will be maintained at Cooper Hospital/ University Medical Center according to their standard procedures. No disposal is contemplated, except for individuals who are withdrawn from the study (either voluntarily or otherwise), in which case the health questionnaires held at Cooper, and samples and associated data held at Coriell will be destroyed. Otherwise, encoded/ tabulated data without personal identifiers of just the subset of samples that will be submitted to the NIA Cell Repository will be maintained in the secure files of The Coriell Institute for Medical Research indefinitely.

13. Modification of the protocol: As this is not an IND/ IDE protocol, no modifications are anticipated, with the possible exception of the recruitment of additional subjects. This might be necessary to achieve statistical validity of possible correlations between the genetic polymorphisms and clinical data. The use of additional methods to recruit subjects might be considered if targets are not met. If this becomes necessary, the revisions, including any proposed new recruiting methods, will be submitted to the Institutional Review Boards of both local institutions, and subsequently to the OTSG HSRRB for approval.

14. Departure from the Protocol: Any departures from the proposed protocol with respect to the consents, questionnaires, or specimens will be submitted to the Institutional Review Boards of both local institutions, and subsequently to the OTSG HSRRB.

15. Roles and Responsibilities of Study Personnel: See (i) above.

16. USAMRMC Volunteer Registry Database: Project judged not greater than minimal risk by local review boards, therefore not applicable.

Signature of Principal Investigator: _____
David K. Moscatello, Ph.D.

Date: _____

STATISTICAL ANALYSIS PLAN

Our analyses will be based on samples obtained from 300 prostate cancer patients (prospectively collected) and from approximately 200 controls (from existing panels). The study's aims are to evaluate

- (1) the association between EGFR intron 1 CA repeats and prostate cancer;
- (2) the association between AR CAG repeats and prostate cancer; and
- (3) the combined (synergistic) effect of EGFR and AR on prostate cancer.

The first two aims pertain to the main effect of each gene, while the third aim focuses on their possible interaction. Preliminary analyses will be based on two-by-two cross-classification tables of each gene with prostate cancer status (case/control). We will estimate and test the (crude) unadjusted odds ratio separately for each gene, using Fisher's exact test and Mantel-Haenszel stratification analysis. We will then model the outcome (prostate cancer case or control status) as a function of both genes via logistic regression. In this multivariable analysis, we will also control for age, race, and other potential confounders.

Finally, we will test the hypotheses of "no multiplicative interaction" and "no additive interaction" between the two genes. Using the long-EGFR/long-AR combination as the referent group, the hypothesis of no multiplicative interaction implies that the joint odds ratio for the short-EGFR/short-AR combination is equal to the product of the two main effects odds ratio (i.e., short-EGFR/long-AR and long-EGFR/short-AR). The test of this hypothesis involves testing the product interaction term; likelihood ratio and Wald tests are straightforward to compute in all statistical packages. The hypothesis of no additive interaction, on the other hand, implies that the joint odds ratio is the sum of the two main effects odds ratios minus one. Although preprogrammed software capabilities do not allow testing of this hypothesis in logistic regression, we have a SAS macro that will allow us to perform the corresponding likelihood ratio and Wald tests.

We have also planned secondary analyses to assess:

1. the effects of the two genes among Caucasian and African-American subjects (i.e., gene-by-race interactions); and
2. the association between the length of the repeats for each gene and cancer recurrence and/or survival (among the prostate cancer cases only).

SAMPLE SIZE AND POWER

Based on previous data, EGFR intron 1 CA repeats show a distribution with 3 peaks in the general population, at 20, 18 and 16 repeats. A smaller number of repeats (<17, approximately 45% in the general population) are hypothesized to be associated with higher risk of prostate cancer. With 300 cases and 200 controls, using a two-tailed Fisher's exact test with alpha of 0.05, we have 84% power to detect an odds ratio of about 1.75 (i.e., short allele in 45% of the controls vs. 59% of the cases).

Similarly, based on previous data, AR CAG short repeats (<20) seem to be present in about 30% of the general population. With 300 cases and 200 controls, using a two-tailed Fisher's exact test with alpha of 0.05, we have 82% power to detect an odds ratio of 1.75 (i.e., short allele in 30% of the controls vs. 43% of the cases).

In terms of the interaction between the two genes, we have good power to detect moderate interactions on both the additive and the multiplicative scale. All power calculations were performed via Monte-Carlo simulation, using the appropriate likelihood ratio tests in logistic regression, with alpha of 0.05.

Assuming main effect odds ratios for each gene of about 1.75, under the "no additive interaction hypothesis", we expect a joint odds ratio of 2.5 (i.e., $1.75+1.75-1$) for the comparison of the short-EGFR/short-AR combination with the referent long-EGFR/long-AR combination. In our study, we have power to detect departures from additivity when the synergy factor is 3 or higher (i.e., an odds ratio for the joint effect of 5.5 or higher):

Allele ^{*****}	Effect [°]	OR ^{*****}	OR [°]	Power ^{*****}	OR [°]	Power
EGFR [°]	AR ^{*****}	type ^{*****}				
long [°]	long ^{***}	refer. ^{****}	1.00			
long [°]	short [°]	main ^{*****}	1.75			
short	long ^{***}	main ^{*****}	1.75			
short	short [°]	joint ^{*****}	2.50 ^{*^{***}}	5.5 ^{***}	81%	6.5 ^{***} 91%

(*) Additivity of effect (i.e., no additive interaction)

With the same assumptions of main effect odds ratios for each gene of about 1.75, under the "no multiplicative interaction hypothesis", we expect an odds ratio of 3.06 (i.e., 1.75×1.75) for the comparison of the short-EGFR/short-AR combination with the referent long-EGFR/long-AR combination. In our study, we have power to detect a multiplicative interaction factor of about 3 or higher (i.e., an odds ratio for the joint effect of 9 or higher):

Allele ^{*****}	Effect [°]	OR ^{*****}	OR [°]	Power ^{*****}	OR [°]	Power
EGFR [°]	AR ^{*****}	type ^{*****}				
long [°]	long ^{***}	refer. ^{***}	1.00			
long [°]	short [°]	main ^{*****}	1.75			
short	long ^{***}	main ^{*****}	1.75			
short	short [°]	joint	3.06 ^{*^{***}}	9.2 ^{***}	75% ^{***}	10.7 ^{***} 85%

(*) Multiplicativity of effect (i.e., no multiplicative interaction)

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PRESENT ACADEMIC APPOINTMENT:

1999- Assistant Professor and Supervisor, Differentiated Cell Laboratory, Coriell
Institute for Medical Research, Camden, NJ

EDUCATION:

1975-84 Ph.D., Biological Sciences, Purdue University, W. Lafayette, Indiana.

1971-75 B.S., Microbiology, Pennsylvania State University, University Park,
Pennsylvania. With Distinction.

PREVIOUS ACADEMIC APPOINTMENTS:

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1984-1987 Visiting Instructor of Microbiology, Dept. of Biological Sciences, Purdue
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OTHER PROFESSIONAL ACTIVITIES:

2001- Primary Investigator, Department of Defense Prostate Cancer Research Program
Grant, PC001407 "Epidermal growth factor (EGF) receptor intron 1 repeat
polymorphisms in African-American and Caucasian males: Influence on prostate

cancer risk or disease progression and interaction with androgen receptor CAG repeat polymorphisms", \$75,000 direct annually for 3 years, 40% effort

- 2001-2002 Novel Methods for the Isolation, Culture, and Cryopreservation of Human Adipocytes and Adipose Stromal Cells from Tumescant Liposuction Procedures. American Society for Dermatologic Surgery, \$15,000 direct, 11/01/01 - 10/31/02.
- 1999-2009 NO1-AG-1-2101 (Dr. Robert T. Johnson, P.I.) Selection, Production, Characterization, and Distribution of Genetically Marked Cells for Aging Research, National Institute on Aging, 1/31/00-12/31/09, 20% effort
- 1995-97 Co-investigator, NIH RAID grant, Safety and Immunological responses to immunotherapy in patients with solid tumors using a peptide derived from a tumor specific variant of the epidermal growth factor receptor
- 1995-97 Co-investigator, CaP CURE award, Study of the role of the EGF receptor and GM-CSF receptor β -chain receptor complex in prostate cancer
- 1990-1997 Board member, Atlantic County Unit, American Cancer Society
- 1994 Co-chairperson for "Tyrosine Kinases and Phosphatases" Minisymposium at AACR Annual Meeting.

HONORS AND AWARDS:

- 1995-97 National Institutes of Health Postdoctoral Research Fellowship
- 1990 Stockton State College Distinguished Faculty Fellowship
- 1980-81 David Ross Graduate Fellowship

MEMBERSHIP IN SCIENTIFIC ASSOCIATIONS:

- 2002- American Society for Cell Biology
- 1998- American Association for Cancer Research
- 1987- American Association for the Advancement of Science
New York Academy of Sciences

PRESENTATIONS:

New Cells for New Technologies: Differentiated Cells, Multipotent Adult Stem Cells, and Embryonic Stem Cells , ISBER Annual Meeting Reception, Coriell Institute, Camden, NJ, May 5, 2003.

The Promise of Biotechnology: Multipotent Adult Stem Cells and Embryonic Stem Cells , Drew University Board of Visitors, Madison, NJ, April 23, 2003.

David K. Moscatello, Ph.D.

Serum-Free Culture of Keratinocytes and other Epithelial Cells , Department of Dermatology, Thomas Jefferson University, Philadelphia, PA, March 17, 2003.

"Fat Transfer: Laboratory Analysis", American Society for Dermatologic Surgery (ASDS) Annual Meeting, Chicago, IL, November 2, 2002.

"Novel Methods for the isolation, culture, and cryopreservation of human adipocytes and adipose stromal cells from tumescent liposuction procedures" ASDS Annual Meeting, Chicago, IL, November 1, 2002. "Adult Multipotent Stem Cells", Coriell Institute for Medical Research Board of Trustees Meeting, Camden, NJ, July 9, 2002

"Sailing the Islets of Langerhans: Research approaches to increasing the supply of pancreatic islets for diabetes treatment", Staff Seminar, Coriell Institute for Medical Research, Camden, NJ, December 4, 2001.

"Sailing the Islets of Langerhans, Floating in Fat: The promise of multipotent stem cells", Richard Stockton College of New Jersey, Pomona, NJ, November 14, 2001.

"Evidence for a PI 3-kinase and JNK dependent but Akt independent cell survival pathway", AACR Annual Meeting, San Francisco, CA, April 4, 2000.

The extracellular matrix proteoglycan decorin inhibits tumor cell growth by activation of the EGF receptor , East Coast Connective Tissue Society, Philadelphia, PA, March 28, 1998.

Mechanism of tumor cell growth suppression by the extracellular matrix proteoglycan decorin: Involvement of the EGF receptor , Thomas Jefferson University, Philadelphia, PA, September 19, 1997.

Expression of a variant epidermal growth factor receptor in Barrett s esophagus and gastric adenocarcinomas, AACR Annual Meeting, San Diego, CA, April 14, 1997.

Phosphatidylinositol 3-kinase activation by a naturally occurring variant EGF receptor, Keystone Symposium Temporal & Spatial Determinants of Specificity in Signal Transduction, Keystone, CO, April 4, 1997.

Constitutive activation of phosphatidylinositol 3-kinase by a naturally occurring EGF receptor variant. Thomas Jefferson University, Philadelphia, PA, December 20, 1996.

"High-level expression of a mutant epidermal growth factor receptor induces cell-specific alterations in signal transduction. AACR Annual Meeting, Washington, DC, April 24, 1996.

"Cell type - specific alterations in signal transduction induced by high-level expression of a mutant EGF receptor. Keystone Symposium Signal transduction through tyrosine kinases , Taos, NM, March 28, 1996.

"Transformation and altered signal transduction by a mutant EGF receptor from human tumors. Research in Progress Seminar, Thomas Jefferson University, March 22, 1996.

Signal transduction pathways are altered in cells transformed by a mutant EGF receptor from human tumors , Cold Spring Harbor Symposium Tyrosine Phosphorylation & Cell Signaling , May 3 - 7, 1995

Mutant human EGF receptors as targets for peptide immunotherapy , AACR Annual Meeting, Toronto, Canada, March 20, 1995.

PATENT APPLICATIONS:

"Sensitive Detection of Wild-Type and Mutant EGFR by Specific Elisa Assays in Any Biological Sample", Kim Leitzel, David K. Moscatello, Alan Lipton, and Albert J. Wong, co-inventors. U.S. patent application submitted March 2000.

"Reagents and Processes for Targeting Mutant Epidermal Growth Factor Receptors", Albert J. Wong and David K. Moscatello, co-inventors. U.S. and international patents pending.

PUBLICATIONS:

1. Modjtahedi, H., **Moscatello, D.K.**, Box, G., Green, M., Shotton, C., Lamb, D.J., Reynolds, L.J., Wong, A.J., Dean, C., Thomas, H., and Eccles, S. Targeting Of Cells Expressing Wild Type EGFR And Type-III Mutant EGFR (EGFRvIII) By Anti-EGFR Mab ICR62: A Two-Pronged Attack For Tumour Therapy. *Int J Cancer* 105(2), 273-80, 2003.
2. Antonyak M.A., Kenyon L.C., Godwin A.K., James D.C., Emlet D.R., Okamoto I., Tnani M., Holgado-Madruga M., **Moscatello D.K.**, Wong A.J. Elevated JNK activation contributes to the pathogenesis of human brain tumors. *Oncogene* 21(33): 5038-5046, 2002.
3. Olapade-Olaopa, E.O., Ogunbiyi, J.O., MacKay, E.H., Muronda, C.A., Alonge, T.O., Danso, A.P., **Moscatello, D.K.**, Sandhu, D.P., Shittu, O.B., Terry, T.R., Wong, A.J., and Habib, F.K. Further characterization of storage-related alterations in immunoreactivity of archival tissue sections and its implications for collaborative multicenter immunohistochemical studies. *Appl. Immunohistochem. Mol. Morphol.* (3): 261-266, 2001.
4. **Moscatello, D.K.** and Iozzo, R.V. Interaction of Proteoglycans with Receptor Tyrosine Kinases. *In Proteoglycan Protocols, Methods in Molecular Biology* 171, Renato V. Iozzo, Ed. Humana Press, Totowa, New Jersey, pp. 427-434, 2001.
5. Tang, C.K., Gong, X-Q., **Moscatello, D.K.**, Wong, A.J., and Lippman, M.E. EGFRvIII enhances tumorigenicity in Human Breast Cancer. *Cancer Research*, 60, 3081-3087, 2000.
6. Olapade-Olaopa E.O., **Moscatello, D.K.**, MacKay, E.H., Horsburgh, T., Sandhu, D.P.S., Terry, T.R., Wong A.J., and Habib F.K. Evidence for the differential expression of a variant EGF receptor protein in human prostate cancer. *British Journal of Cancer*. 82(1), 186-194, 2000.
7. Maroun C.R., **Moscatello, D.K.**, Naujokas, M.A., Holgado-Madruga, M., Wong, A.J., Park, M. A conserved inositol phospholipid binding site within the pleckstrin homology domain of the Gab1 docking protein is required for epithelial morphogenesis. *J. Biol. Chem.* 274(44), 31719-31726, 1999.
8. Iozzo, R.V., **Moscatello, D.K.**, McQuillan, D.J., and Eichstetter, I. Decorin is a biologically ligand for the Epidermal Growth Factor Receptor. *J. Biol. Chem.* 274, 4489-4492, 1999.
9. Antonyak, M., **Moscatello, D.K.**, and Wong, A.J. Constitutive activation of c-Jun N-terminal kinase by a mutant epidermal growth factor receptor. *J. Biol. Chem.* 273, 2817-2822, 1998.
10. **Moscatello, D.K.**, Santra, M., Mann, D.M., McQuillan, D.J., Wong, A.J., and Iozzo, R.V. Decorin suppresses tumor cell growth by activating the epidermal growth factor receptor. *J. Clin. Invest.* 101, 406-412, 1998.

11. **Moscatello, D.K.** and Wong, A.J. Constitutive activation of phosphatidylinositol 3-kinase by a naturally occurring mutant epidermal growth factor receptor. *J. Biol. Chem.* 273, 200-206, 1998.
12. Emlet, D.R., **Moscatello, D.K.**, Ludlow, L.B., and Wong, A.J. Subsets of epidermal growth factor receptors during activation and endocytosis. *J. Biol. Chem.* 272, 4079-4086, 1997.
13. Montgomery, R.B., **Moscatello, D.K.**, Wong, A.J., and Stahl, W.L. Epidermal growth factor receptor stimulation of diacylglycerol kinase. *Biochem. Biophys. Res. Comm.* 232, 111-116, 1997.
14. Holgado-Madruga, M., **Moscatello, D.K.**, Emlet, D.R., Dieterich, R., and Wong, A.J. Gab1 mediates phosphatidylinositol 3-kinase activation and the promotion of cell survival by nerve growth factor. *Proc. Natl. Acad. Sci. USA.*, 94, 12419-12424, 1997.
15. **Moscatello, D.K.**, Ramirez, G., and Wong, A.J. A naturally occurring mutant human epidermal growth factor receptor as a target for peptide vaccine immunotherapy of tumors. *Cancer Res.* 57, 1419-1424, 1997.
16. **Moscatello, D.K.**, Montgomery, R.B., Sundareshan, P., McDanel, H., Wong, M.Y., and Wong, A.J. Transformation and altered signal transduction by a naturally occurring mutant EGF receptor. *Oncogene* 13, 85-96, 1996.
17. Holgado-Madruga, M., Emlet, D.R., **Moscatello, D.K.**, Godwin, A.K., and Wong, A.J. A Grb2-associated docking protein in EGF- and insulin-receptor signalling. *Nature* 379, 560-564, 1996.
18. Montgomery, R.B., **Moscatello, D.K.**, Wong, A.J., Cooper, J.A., and Stahl, W.L. Differential modulation of MEK and MAP kinase activities by a mutant EGF receptor. *J. Biol. Chem.* 270, 30562-30566, 1995.
19. **Moscatello, D.K.**, Holgado-Madruga, M., Godwin, A.K., Ramirez, G., Gunn, G., Zoltick, P.W., Biegel, J.A., Hayes, R.L., and Wong, A.J. Frequent expression of a mutant Epidermal Growth Factor receptor in multiple human tumors. *Cancer Res.* 55, 5536-5539, 1995.
20. Reist, C., Archer, G.E., Kurpad, S.N., Wikstrand, C.J., Vaidyanathan, G., Willingham, M.C., **Moscatello, D.K.**, Wong, A.J., Bigner, D.D., and Zalutsky, M.R. Tumor-specific anti-Epidermal Growth Factor receptor variant III monoclonal antibodies: Use of the tyramine-cellobiose radioiodination method enhances cellular retention and uptake in tumor xenografts. *Cancer Res.* 55, 4375-4382, 1995.
21. Wikstrand, C.J., Hale, L.P., Batra, S.K., Hill, M.L., Humphrey, P.A., Kurpad, S.N., McLendon, R.E., **Moscatello, D.**, Pegram, C.N., Reist, C.J., Traweck, S.T., Wong, A.J., Zalutsky, M.R., and Bigner, D.D. Monoclonal antibodies against EGFRvIII are tumor specific and react with breast and lung carcinomas and malignant gliomas. *Cancer Res.* 55, 3140-3148, 1995.

REFERENCES AND FURTHER INFORMATION AVAILABLE UPON REQUEST

Biographical Sketches

Provide the following information for the key personnel listed on page 1 of the Detailed Cost Estimate form for the initial budget period.

NAME

JOEL LESLIE MARMAR, M.D.

POSITION/TITLE

Professor of Urology and Head,
Division of Urology, Department of Surgery

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include post-doctoral training.)

INSTITUTION AND LOCATION

DEGREE
(IF APPLICABLE)

YEAR(S)

FIELD OF STUDY

Franklin and Marshall College, Lancaster, PA

B.S.

1960

Biology

University of Pennsylvania School of Medicine
Philadelphia, PA

M.D.

1964

Medicine

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past 3 years and to representative earlier publications pertinent to this application. If the list of publications in the last 3 years exceeds two pages, select the most pertinent publications. PAGE LIMITATIONS APPLY. DO NOT EXCEED THREE PAGES FOR THE ENTIRE BIOGRAPHICAL SKETCH PER INVESTIGATOR.

1964-65 INTERNSHIP, Rotating, Albert Einstein Medical Center, Philadelphia, PA

1965-66 RESIDENCY: General Surgery, Jeanes Hospital, Fox Chase, Pennsylvania

1966-69 RESIDENCY: Urology, Temple University Hospital, Philadelphia, PA

1969-71 Major/Medical Corps, U.S. Army, Chief of Urology, 24th Evacuation Hospital,
Vietnam

1984 - Present Professor of Urology, University of Medicine and Dentistry of New Jersey, Robert
Wood Johnson School of Medicine at Camden

1993 - Present Medical Director, Fertility Testing Laboratory, Philadelphia, PA

CERTIFICATION:

Urology, 1973 - American Board of Urology

Fellow, 1974 - American College of Surgeons

OTHER TRAINING:

Urologic Microsurgery Course. September 1980 University of Louisville, Louisville, Kentucky

Urologic Laser Surgery Course, September 1983, Temple University Hospital, Philadelphia, PA

Lithotripter Training, November 4-9, 1985, EDAP Instrument, Hospital Pont de Choisy, Paris, France
Dornier HM3, Hospital Necker, Paris, France

RESEARCH AND PROFESSIONAL EXPERIENCE (CONTINUED). PAGE LIMITATIONS APPLY.
DO NOT EXCEED THREE PAGES FOR THE ENTIRE BIOGRAPHICAL SKETCH PER INVESTIGATOR.

OTHER TRAINING (Cont'd.): Additional Lithotripter Training, November 13-20, 1988
Direx Instrument,
University de Liege au Bart Tilman, Liege, Belgium
University Hospital, Maastrik, Holland
Jeanne d'Arc Polyclinic, Lyon, France

Laparoscopy Training, Worldwide Veterinary Services
Parsippany, NJ March 1991

Laser Prostatectomy Training, May 1992
J.R. Bard Co., Chicago, Illinois May 1992

Prostate Cryosurgery Training, January 28 - February 1, 1994
Widdington Hospital (Graham Watson, M.D.), London, England

Prostate Surgery with TUNA (transurethral needle ablation)
Philadelphia, PA June 1, 1997

HONORS AND AWARDS: Phi Beta Kappa, 1960
Student Research Award, 1964
Undergraduate Medical Society
University of Pennsylvania School of Medicine

Certificate of Appreciation (Vietnam Service) 1970
Armed Forces of the United States

Recognition Award, 1983, Leadership in the Field of Andrology
Cooper Hospital/University Medical Center

LICENSURE: State of New Jersey - MA24609
State of Pennsylvania - MD008116E
State of Florida - ME0015259

MILITARY SERVICE: Major/Medical Corps
United States Army, 1969-71
Chief of Urology, 24th Evacuation Hospital, Vietnam

Biographical Sketch

NAME Constantine Daskalakis		POSITION TITLE Assistant Professor	
EDUCATION <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
University of Athens (Greece)	B.S.	1989	Biology
University of Massachusetts (Amherst, MA)	M.S.	1992	Epidemiology
Harvard University (Boston, MA)	Sc.D.	1997	Biostatistics & Epidemiology

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Key personnel include the principal investigator and any other individuals who participate in the scientific development or execution of the project. Key personnel typically will include all individuals with doctoral or other professional degrees, but in some projects will include individuals at the masters or baccalaureate level provided they contribute in a substantive way to the scientific development or execution of the project. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. DO NOT EXCEED TWO PAGES.

Professional Experience:

2000 - Present Assistant Professor, Department of Medicine, Thomas Jefferson University
 1997 - 2000 Research Fellow, Department of Biostatistics, Harvard University
 1993 - 1996 Teaching Fellow, Department of Biostatistics, Harvard University
 1992 - 1996 Research Assistant, Department of Epidemiology, Harvard University
 1987 - 1991 Research Assistant, Department of Biostatistics & Epidemiology, University of Massachusetts

Honors and Awards:

1995 Teaching Assistant of the Year Award, Harvard School of Public Health
 1994 Robert B. Reed Prize of Biostatistics, Department of Biostatistics, Harvard School of Public Health

Publications:

Zahner GEP, **Daskalakis, C.** Modeling sources of informant variance in parent and teacher ratings of child psychopathology. *Int J Meth Psych Res* 1998; 7: 3-16.

Zahner GEP, **Daskalakis C.** Factors associated with mental health, general health, and school-based service use for child psychopathology. *Am J Public Health* 1997; 87: 1440-1448.

Hauser R, **Daskalakis C**, Christiani DC. Regression approach to the analysis of serial peak flow among fuel oil ash exposed workers. *Am J Respir Crit Care Med* 1996; 154: 974-980

Fitzmaurice GM, Laird NM, Zahner GEP, **Daskalakis C.** Bivariate logistic regression analysis of childhood psychopathology ratings using multiple informants. *Am J Epidemiol* 1995;142: 1194-1203.

Daskalakis C, Goldberg RJ, Ockene JK, Kalan K, Hosmer DW, Pbert L. Comparison of patients' and their resident physicians' responses regarding smoking-cessation interventions. *Acad Med* 1993; 68: 168-170.

Daskalakis C, Shenassa ED. The connection between R^2 and sensitivity and specificity in the case of a dichotomous outcome. *The American Statistician* (submitted).

Daskalakis C, Murphy JM, Laird NM. Multivariate analysis of outcomes from multiple sources: A short-interval study of depression. *Am J Epidemiol* (submitted).

Daskalakis C, Lard NM, Lipsitz SR. Simultaneous modeling of mean response and association for multivariate categorical outcomes. *Biostatistics* (submitted).

Daskalakis C, Lipsitz SR. Assessing additive interactions in logistic regression. *Biometrics* (submitted).

Juliette M. May

PII Redacted

Home: (856) 742-9279
Work: (856) 963-3577

OBJECTIVE: To secure a challenging public-spirited position in a fast-paced environment, which requires well-developed interpersonal skills, analytical ability and attention to detail that is conducive to professional and personal growth.

PROFESSIONAL EXPERIENCE:

Cooper Health System

10/00-Present

Practice Coordinator of Urology

Practice Coordinator to the Assistant Professor of the Department of Surgery, Division of Urology. Coordinator of the Prostate Cancer Program – Daily interaction with patients and physicians, conducting surveys regarding Radioactive Seed Implantation. Duties also include scheduling of surgeries, heavy telephone volume, verifying insurance information and retrieving referrals using the Envoy / IDX Computer System.

Temple University Health System

3/98- 10/00

Executive Administrative Assistant II-Office Manager

Responsible for providing administrative support to the Medical Director, Vice President, and Nursing Staff of TUHS Medical Management department, as well as the Ambulatory Care/Disease Management department personnel. Principle duties include, but are not limited to, interacting with all levels of personnel. Exhibiting tact and diplomacy; dictation, exercising professional judgement and acting independently in managing matters of a confidential nature; meeting coordination and travel planning/organizing; expense tracking and screening all incoming correspondence/telephone calls, taking the appropriate actions when necessary. Accountable for departmental payroll processing, patient transportation/troubleshooting. Participates as an active member of the Diabetes Disease Management Committee.

Law Offices of Louis Agre

7/96-2/98

Legal Secretary / Administrative Assistant – Part- Time

Secured and prepared all documents for court hearings, typed all correspondence and legal documents, communicated with clients, including preparation for deposition. Responsible for Data Entry, Filing, and Faxing.

Law Offices of David Oh

9/92-6/96

Legal Secretary / Office Manager

Synchronized special events and fundraisers, typed all correspondence and legal documents. Handled all billing accounts, payroll and banking deposits. Filed documents with the Courts. Accountable for ordering company supplies and all troubleshooting.

EDUCATION:

Temple University –

9/99- Present

Major – Computer Programs– Certificates in PowerPoint- Access- Word-Excel - Spanish

The Craft Medical Institute -

9/92 – 6/93

Certificate in Medical Assisting – CPR Certified – EKG- Phlebotomy- Medical Terminology

RELATED SKILLS:

Proficient at executing multiple tasks with critical deadlines and objectives. Exceptional reasoning and phone management skills. Effective oral and written communication skills. Typing Speed 65wpm. Ability to prioritize to ensure timely and accurate completion of all work. Well organized with professional attention to detail. Demonstrated ability to adapt to environments of diversity. Knowledge of clinical procedures and medical terminology. Proficient with major word processing software: Certificates in Microsoft (Word, Excel, PowerPoint, Outlook and Access), IBX Phone System – Spanish Speaking Skills, Data Entry, and Bookkeeping.

References Furnished Upon Request

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Page 1 of 5

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

TITLE OF STUDY: Development of a regional prostate cancer registry & risk assessment program

DEPARTMENT: Cooper Cancer Institute; Coriell Institute for Medical Research (Moscatello)

PRINCIPAL INVESTIGATOR : Joel Marmar, MD

PHONE NUMBER : (856) 963-3577

CO-INVESTIGATOR(S): Generosa Grana, MD, David K. Moscatello, Ph.D., Juliette M. May

PHONE NUMBER(S): (856) 342-2439; (856) 966-5054; and (856) 963-3577, respectively

SUBJECT'S NAME: _____

SUBJECT'S ADDRESS : _____

DATE OF BIRTH: _____

The doctors at the Cooper Health system do research on the nature of diseases and new treatments. This research project is to study the effect of environmental, life styles and genetic causes of prostate cancer. No one can say that you are going to be helped by it. If you have any questions or problems during the study you can call the doctors at the Phone numbers listed at the top of this page and they will try to help you. If you want to know more about their backgrounds, you can get the information from the Medical Staff office at the Cooper Health System. Information on The Coriell Institute for Medical Research or Dr. Moscatello can be obtained at Coriell (403 Haddon Avenue, Camden, NJ 08103; Dr. Moscatello's email: dmoscate@cimr.umdj.edu) or on the web at <http://coriell.umdj.edu/>.

PURPOSE OF STUDY: The Cooper Cancer Institute at Cooper Hospital/ University Medical Center and its collaborators are conducting research on the causes of Prostate cancer to find new methods of prevention, diagnosis and treatment. Prostate cancer is one of the leading causes of cancer among men and is second only to lung cancer. Since prostate cancer is more frequent in African Americans than Caucasians, it is important to recruit men of all races into this study.

This study will involve the development of a prostate cancer database that will collect data not currently available on prostate cancer patients and their family members. Personal information, blood and tissue samples will be collected from participants. Researchers, including scientists at Coriell, who would like to study possible causes of cancer such as genes, lifestyles and environmental factors will use the samples and information. It is estimated that 100 participants a year and approximately 300 participants over a 3 year period will be enrolled in this study.

Subject's initials _____

Witness's initials _____

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STUDY PROCEDURES: You have been told that during the course of this study, the following will occur: Each participant will be asked to provide lifestyle, medical and family history information and a blood sample. Participants who have had a biopsy, either benign (noncancerous) and/or malignant (cancer) will be asked for a tissue sample. Specifically we will ask you to do the following:

1. Complete a questionnaire on your family history of cancer, as well as medical and lifestyle information. You may refuse to answer any question on the questionnaire that makes you uncomfortable.
2. Donate three tubes of blood (about 2-3 tablespoons) that will be drawn from a vein in your arm. You may be asked to donate blood samples periodically throughout the study, but no more than once per year.
3. If you have had a biopsy, or surgery to remove a tumor, or are scheduled for surgery, we will ask you to complete an authorization form. This form will allow us to obtain copies of your pathology and medical records. It will also allow us to obtain a portion of your fresh tissue or stored tissue (after surgery, tissue samples are stored in wax blocks at the hospital).
4. Complete a follow-up questionnaire each year for four years to update the registry files on your health and to reconfirm your willingness to participate in the study. (Subjects who enroll on the 3rd year will receive 1 year follow-up.)

You are eligible for this study because you meet one of the following criteria: 1) you have a diagnosis of prostate cancer or 2) you have a family history of cancer or 3) you are of the African-American race.

It is possible that a genetic link to prostate cancer will be discovered. It is also possible that you will be discovered to have a gene that may be linked to an increased risk of developing prostate cancer. It is your option to be told or not told this information. You are being asked to make that choice in this form by circling the "Yes" or "No" that follow. "Yes" means you want to be told. "No" means you do not want to be told. Please circle and initial your preference.

Yes or No _____ initials

If you choose not to be told no other informative action will be taken. However if you choose to be informed and information about you is discovered, a letter asking you to make an appointment with the researchers will be sent to your home. During this appointment, you will be informed of the findings and offered counseling/education on the subject.

BENEFITS: Although you will receive no immediate benefit from your participation in the study, investigators hope that the knowledge gained from future research studies will be of benefit to you, your relatives, and future generations.

Subject's initials _____

Witness's initials _____

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RISK AND DISCOMFORTS: The risk of discovering that you have a genetic predisposition to cancer will be discussed with you prior to agreeing to participate in the study. This may cause you concern. You may also have concerns even if you are not in the future told that you have a gene alteration that has been linked to an increased risk of prostate cancer. You do not have to agree to have this information revealed to you or your family members. Some people are concerned about genetic discrimination by insurance companies and/or employers. We will not release any information about you or your family to an insurance company or employer without your consent. The risks and discomfort associated with giving blood include the possibility of bleeding and bruising. This rarely causes a severe problem.

ALTERNATIVES: The alternative is to not participate in this study.

COSTS/COMEPENSATION: Your participation in this study is free. Any counseling/ education sessions provided to you at Cooper in connection with this study will also be free. The cost of any counseling or education you choose to receive somewhere other than Cooper or not in connection with this study will be your responsibility. You will not be paid for your participation in the study.

SAMPLE DONATION: During this study, you will be asked to provide blood (and prostate, if biopsy or surgery is medically indicated) samples. These samples will be used for isolation of DNA, RNA, and proteins for analysis, immunohistochemical analysis, and for the establishment of cell lines, and may also be used for purposes that are currently unknown. There is a chance that the samples that you are donating under this study may be used in other research studies and may have some commercial value. Should your donated sample(s) lead to the development of a commercial product, the institution(s) or inventor(s) who developed the product will own it and may take action to patent and license the product. The Institute does not intend to provide you with any compensation for your participation in this study nor for any future value that the sample you have given may be found to have. You will not receive any notice of future uses of your sample(s). You are being asked to make the choice in this form by circling the "Yes" or "No" that follow. "Yes" means you agree to allow any sample(s) collected for this study to be used for further research. "No" means you do NOT want your sample(s) to be used for any further research other than this study. Please circle and initial your preference.

Yes or No _____ initials

CONFIDENTIALITY: Every effort will be made to maintain the confidentiality of your study records. All identifying markers such as your name and address will be removed from all your information and samples, and a code number will be used instead. The list of names and matching code numbers will be stored securely in a safe and kept separately from the other study information. Only the principal investigator or other hospital personnel he may designate will have access to this list. Your blood and tissue samples labeled with only your code number will be stored securely and indefinitely at the Coriell Institute for Medical Research in Camden New Jersey. Officials of the Cooper Health System, including the Institutional Review Board and the Coriell Institute for Medical

Subject's initials _____

Witness's initials _____

Cooper Hospital/University Medical Center

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Research may inspect sections of your medical records related to this study. If the findings from the study are published, you will not be identified by name. Your identity will remain confidential unless disclosure is required by law. It should be noted that representatives of the U.S. Army Medical Research and Materiel Command, and of Health and Human Services are eligible to review research records as part of their responsibility to protect human subjects in research. Otherwise your medical record and the information it contains may not be furnished to anyone unaffiliated with the Hospital without your written consent. If your record is used or reviewed for government purposes, your privacy will be protected as much as possible under the laws relating to public revealing of information and the law enforcement responsibilities of the agency. The New Jersey Genetic Act (PL 96, C. 126) regulates genetic testing and also protects against unfair discrimination by both employers and the insurance industry.

CIRCUMSTANCES UNDER WHICH YOUR PARTICIPATION MAY BE TERMINATED

WITHOUT YOUR CONSENT: Your participation may be terminated without consent if you are not available to follow-up or the researchers are unable to contact you for further evaluation.

NEW FINDINGS: During the course of the study, you will be told about any new information that may affect your willingness to remain in the study. The risk of discovering that you have a genetic predisposition to cancer will be discussed with you prior to agreeing to participate in the study. You do not have to agree to have this information revealed to you or your family member.

INJURY: If you are injured as a result of participating in this study, treatment will be available at the Cooper Health System. However, this statement does not mean that costs for such treatment will necessarily be free. In the unlikely event of an injury, you or your insurance company will be billed in the customary manner. Furthermore, no provisions have been made for compensation in the event of injury. No money will be provided by the hospital for compensation for a research related injury. If you believe that you have suffered injury or illness due to your participation in this study, you should notify the Senior Vice President for Academic Affairs or her designee at 856-963-3835. A review by a committee will be arranged to determine if the injury or illness is a direct result of participation in this research. You should also contact that person if you have any questions about your rights as a research subject or if you believe that you have not been adequately informed as to the risks, benefits, alternative procedures, or that you are being pressured to continue in this study against your wishes. You should also understand that this is not a waiver or release of your legal rights. You should discuss this issue thoroughly with the principal investigator or his representative before you enroll in this study.

VOLUNTARY PARTICIPATION: I voluntarily consent to participate in this study. I do so with an understanding of the possible outcomes that might occur in the course of the study. I have had adequate time to read this form and I understand its contents. I have been given a copy for my personal records.

Subject's initials _____

Witness's initials _____

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RIGHT TO REFUSE OR WITHDRAW: I understand that my participation is voluntary and I may refuse to participate or may discontinue my participation at any time, without penalty or loss of benefits to which I am otherwise entitled and without prejudice to my present or future care. I can withdraw by contacting Dr. Joel Marmar's office at the number listed on the first page of this form. I also understand that the investigator has the right to withdraw me from the study at any time. In the event I am no longer participating in the study, blood and tissue samples will be destroyed along with my questionnaire and other materials with my name and code numbers.

INDIVIDUALS TO CONTACT: If I experience side effects or need to discuss any problems or questions concerning my participation in this study, I can contact one of the investigators listed on the first page.

I have read this entire form, or it has been read to me. I have been informed that I have the right to ask questions, and all of my questions regarding this form or this study have been answered to my complete satisfaction. I agree to participate in this research study. I understand by signing this form that I am not waiving any other legal rights to which I might be entitled. I have been given a copy for my personal records.

SIGNATURE OF SUBJECT

Subject Name: _____ Signature: _____

Witness Name: _____ Signature: _____

Date: _____

INVESTIGATOR'S STATEMENT

I have explained the terms and conditions of this consent form to the above named subject including the risk of discovering a genetic predisposition to cancer and based on this conversation I believe he/she has understood what was discussed.

Investigator's Name: _____ Signature: _____

Date: _____

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HIPAA AUTHORIZATION ADDENDUM

AUTHORIZATION TO PERMIT THE USE AND DISCLOSURE OF HEALTH INFORMATION (PROTECTED HEALTH INFORMATION) FOR RESEARCH PURPOSES

RESEARCH STUDY TITLE: Development of a regional prostate cancer registry & risk assessment program

SUB-STUDY TITLE: Epidermal Growth Factor (EGF) Receptor intron 1 CA repeat polymorphisms in African-American and Caucasian males: Influence on Prostate Cancer risk or disease progression and interaction with Androgen receptor CAG repeat polymorphisms

PRINCIPAL INVESTIGATOR: Joel L. Marmar, M.D.
Division of Urology

Phone: 856-963-3577

COINVESTIGATOR(S): Generosa Grana, M.D.,
Hematology/ Oncology

Phone: 856-342-2439

David K. Moscatello, Ph.D.
Coriell Institute for Medical Research

Phone: 856-966-5054

DEPARTMENT(S): Urology (JLM); Hematology/ Oncology (GG); Coriell Institute for Medical Research (DKM)

SPONSOR: Cooper Health System; USAMRMC (Department of Defense, sub-study only)

SUBJECT NAME (PRINT): _____

Why are you being asked to sign this form?

You are being asked to sign this form because the privacy regulations of a law passed by Congress became effective on April 14, 2003. The law is called the Health Insurance Portability and Accountability Act, HIPAA for short. According to the regulations, as a person participating in a research study, you have certain rights concerning your protected health information. You have the right to know what health information will be used and created about you, how this information will be used, and who will have access to it. You have the right to know to whom your health information will be disclosed (released). You also have the right to

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see your own health information. By signing this form you are giving the investigators, their staff, and certain other people specified in this form permission to use your health information for purposes of this research study.

What information will be collected from you for use in this study?

The health information that will be collected from you if you participate in this study includes: Your PSA level from your blood test; any x-ray or other image, or biopsies taken as diagnostic procedures for prostate cancer; specific DNA (genetic) information for the genes encoding the androgen and epidermal growth factor receptors; the Health History Questionnaire; and other information regarding current or future diagnosis or treatment of prostate cancer or benign prostatic hyperplasia. Except for the DNA analysis, these blood tests and x-rays would have been done even if you were not in this research study.

This research study will involve the recording of current and/or future health information from your hospital records and/or your physician's office or other health care provider.

Drs. Marmar and Grana will have access to the information above, but no identified information will be sent to Dr. Moscatello. Dr. Marmar will send the Blood/ tissue and the following info with a code number: Prostate Specific Antigen (PSA) levels, whether or not you have prostate cancer, and if so, the age at diagnosis and the specific diagnosis, and a coded summary of the Health History Questionnaire with all names, addresses, dates of birth or death, and other personal identifiers removed.

How will your health information be used and disclosed?

The information described above will be used to develop a prostate cancer database that will be used by researchers to try to understand the genetic and environmental (lifestyle) factors that contribute to prostate cancer development, as well as the impact prostate cancer has on patients and their family members. Personal information and blood samples will be collected from all participants, and tissue samples will be collected from participants that undergo medically indicated biopsies or surgeries.

All information regarding standard diagnostic tests and treatments will be included in your medical record. However, tests and questionnaires that are done solely for the purpose of this study will be kept only in the study files in Dr. Marmar's office, with the exception of the DNA test results, which will be held without identifying information in the study files by Dr. Moscatello. No information collected solely for study purposes will be distributed to anyone outside Cooper Health System, with the exceptions noted below.

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This research study will result in health information that will be placed into your research study files and medical records. The study files and medical records will be stored in the office of Dr. Joel Marmar and at the Cooper Health System. The health information that will be created about you for the purpose of this study includes Prostate Specific Antigen (PSA) levels, whether or not you have prostate cancer, and if so, the specific diagnosis, and the Health History Questionnaire. If you sign this form, in addition to the Cooper investigators listed on the first page of this authorization form and their research staff, the following people will or may have access to your health information (described above) related to your participation in this research study:

There is an Institutional Review Board (IRB) that oversees research in the Cooper Health System (CHS). Authorized representatives of the CHS IRB may review your health information for the purpose of monitoring the conduct of this research study. The CHS IRB is also registered with the Office of Human Research Protection (OHRP) of the Department of Health and Human Services (DHHS). OHRP is responsible for oversight of programs to protect human subjects in institutions that do research funded by the federal government. Therefore your study records, medical records, and the records of the IRB may also be reviewed by OHRP.

Authorized representatives of the sponsor of the substudy of this research study, the Department of Defense/ U.S. Army Medical Research and Materiel Command, may review and/or obtain your health information held by the Cooper investigators. They will review and/or obtain your health information in order to monitor the accuracy and completeness of the research data and for performing required scientific analyses of the research data. **The study sponsor understands the importance of maintaining the confidentiality of your health information. However, CHS cannot guarantee the confidentiality of this information after it has been obtained by the study sponsor. Any disclosures of your health information by the sponsor will *not* be protected by the federal privacy rules.**

Authorized representatives of CHS or other affiliated health care providers may have access to your health information for the following reasons: (1) to fulfill orders (made by the investigators) for hospital and health care services (e.g., laboratory tests, diagnostic procedures) associated with research study participation; (2) to address correct payment for tests and procedures ordered by the investigators; and (3) for internal hospital operations (i.e. quality assurance).

In unusual cases, the investigators may be required to release your identifiable research information (which may include your study records and other medical record information) in response to an order from a court of law. If the investigators learn that you or someone with whom you are involved is in serious danger or potential harm, they will need to inform, as required by state law, the appropriate agencies.

Will you have access to your health information resulting from participation in this research study?

You may already have a copy of CHS's Notice of Privacy Practices. If you do not have one, the investigator will give you one. This notice says that you are allowed to see information that is in your research study records and medical records that are filed in the offices of your health care provider. For this research study that means the office of the investigators and Cooper Hospital. However, you may not see your health information until the study is finished. You have the right to see information that was created as a result of your participation in this study and information that was collected and used for this research study. If you want to see this information, contact Dr. Joel Marmar.

May you refuse to provide your authorization (permission) for the use of your health information for the purpose of this research study?

Your authorization to use and disclose your health information as described above for the purpose of this research study is completely voluntary. However, if you do not give your written authorization for the use and disclosure of your health information, you will not be allowed to participate or continue to participate in the research study.

If you decide not to give your authorization for the research use and disclosure of your health information, it will not affect your current or future care at CHS, or its affiliated health care providers or hospitals.

May you withdraw your authorization (permission) for the use of your health information for the purpose of this research study?

You may withdraw, at any time, your authorization for the use and disclosure of your health information for the purpose of this research study. However, if you withdraw your authorization for the use and disclosure of your health information, you will also be withdrawn from further participation in this research study. The investigator and research staff will stop collecting health information from you for purposes of the study. In addition, research staff will stop using your health information. They will also stop disclosing (releasing) your information to the parties described above, except to the extent the research staff has relied on information that has already been collected from you. For example, the study staff may need to use or disclose information obtained before you withdrew your authorization in order to preserve the scientific integrity of the study. The investigator also may have to use or disclose your health information to account to the FDA for your withdrawal from the study. You could also decide to give consent for the investigator to continue to collect your health information after you withdraw from the study.

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To formally withdraw your authorization, you should provide a written and dated notice of this decision to the principal investigator of this research study at Joel L. Marmar, M.D., 3 Cooper Plaza, Suite 403, Camden, NJ 08103.

Your decision to withdraw your authorization for the research use and disclosure of your health information will not affect your current or future care at CHS, its affiliated health care providers, or hospitals.

How long will the investigators be permitted to use your health information?

The investigators may continue to use and disclose your health information for the purposes described above for an undetermined period of time. In signing this form, you authorize the use and disclosure of your information for the purposes of this study at any time in the future.

VOLUNTARY CONSENT

All of the above has been explained to me. All of my current questions have been answered. Throughout my participation in this research study, I am encouraged to ask any additional questions I may have about the research use and disclosure of my health information. Such future questions will be answered by one of the investigators listed on the first page of this form.

If I have any questions about my rights associated with the research use of my health information I should call the Senior Vice President for Academic Affairs at 856 963-3835.

By signing this form, I agree to allow the use and disclosure of my health information for the purposes described above. A copy of this authorization form will be given to me.

Subject's Signature

Date

RP#: 97-138 PI: JOEL L. MARMAR, M.D.
Title: Development of a regional prostate cancer registry and risk assessment program

DECLARATION OF DE-IDENTIFICATION (HIPAA)
For Research by Cooper Employees and Medical Staff and/or within CHS
Institutional Review Board

I. Safe Harbor De-identification (45 CFR 164.514(b)(2))

As the investigator creating or receiving a de-identified data set for this study, I certify the following:

- A. To the best of my knowledge, the information used in the study could not be used (alone or with other information) to identify an individual who is a subject of the information, and
- B. None of the following types of information, regarding subjects or relatives, employers, or household members of subjects, are used in this study;
 - 1. Names;
 - 2. All geographic identifiers except state or the first three digits of a zip code.
 - 3. The month and day (the year can be kept) from all dates directly related to an individual, including birth date, admission date, discharge date, date of death. Ages over 89 are combined in a single category of "Age 90 and older."
 - 4. Telephone numbers;
 - 5. Fax numbers;
 - 6. Electronic mail addresses;
 - 7. Social security numbers;
 - 8. Medical record numbers;
 - 9. Health plan beneficiary numbers;
 - 10. Account numbers;
 - 11. Certificate/license numbers;
 - 12. Vehicle identifiers and serial numbers, including license plate numbers;
 - 13. Device identifiers and serial numbers;
 - 14. Web Universal Resource Locators (URLs);
 - 15. Internet Protocol (IP) address numbers;
 - 16. Biometric identifiers, including finger and voice prints;
 - 17. Full face photographic images and any comparable images; and
 - 18. Any other unique identifying number, characteristic, or code, except as permitted

for reidentification.³

C. If I assign a code or other means of record identification to allow de-identified information to be reidentified,

1. The code or other means of record identification is not derived from or related to information about the individual and is not otherwise capable of being translated so as to identify the individual, and
2. I will not use or disclose the code or other means of record identification for any purpose other than re-identification, and I will not disclose the mechanism for re-identification.

D. Before I allow a code to be used to re-identify this information,

1. If the purpose of the re-identification is within the scope of the original protocol, I will obtain approval of an amendment from the IRB and comply with the requirements of HIPAA; or
2. If the purpose of the re-identification is outside the scope of the original protocol, I will submit a full New Study Application, obtain IRB approval, and comply with the requirements of HIPAA.

Investigator's
signature:

Del (Munmar)

Date: 9/9/03

Investigator's position: *Attending staff, Head-Division of Urology*
If PI is a resident or fellow, a faculty advisor's signature is required.

• If required:

Faculty Advisor's signature: _____

Faculty Advisor's name: _____

Date: _____

³ If your research involves an unusual disease or condition, attach a statement explaining 1) the incidence of the disease or condition and 2) the potential of the information in your study to be used to identify the individuals.

If required: Faculty Advisor's signature: _____ Faculty Advisor's name: _____	Date: _____
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For IRB Use Only

DECLARATION OF DE-IDENTIFICATION (HIPAA)
For Research by Cooper Employees and Medical Staff and/or within CHS
Institutional Review Board

The attached Declaration of De-identification has been reviewed and approved. The IRB finds that there is no reasonable basis to believe that the health information used in this study can be used to identify an individual, and therefore is not individually identifiable health information, based on satisfaction of the following requirements:

- ☒ Regulatory de-identification (45 CFR 164.514(b)(2)); or
☐ De-identification shown by statistical analysis, (45 CFR 164.514(b)(1)).

It was reviewed by the following process:

- ☐ Full Board Review; Date: _____
☒ Expedited Review by experienced, designated Board member; Date: 9/9/03
☐ Expedited Review by IRB Chair; Date: _____

Date Approved: 9/9/03
 Reviewer: Shiraz A. Spiegel

RP#: RP-02-046

PI: David K. Moscatello, Ph.D.

Title: Epidermal Growth Factor (EGF) receptor intron 1 CA repeat polymorphisms in African-American and Caucasian males: Influence on Prostate Cancer risk or disease progression and interaction with Androgen Receptor CAG repeat polymorphisms

DECLARATION OF DE-IDENTIFICATION (HIPAA)
For Research by Cooper Employees and Medical Staff and/or within CHS
Institutional Review Board

I. Safe Harbor De-identification (45 CFR 164.514(b)(2))

As the investigator creating or receiving a de-identified data set for this study, I certify the following:

- A. To the best of my knowledge, the information used in the study could not be used (alone or with other information) to identify an individual who is a subject of the information, and
- B. None of the following types of information, regarding subjects or relatives, employers, or household members of subjects, are used in this study;
 - 1. Names;
 - 2. All geographic identifiers except state or the first three digits of a zip code.
 - 3. The month and day (the year can be kept) from all dates directly related to an individual, including birth date, admission date, discharge date, date of death. Ages over 89 are combined in a single category of "Age 90 and older."
 - 4. Telephone numbers;
 - 5. Fax numbers;
 - 6. Electronic mail addresses;
 - 7. Social security numbers;
 - 8. Medical record numbers;
 - 9. Health plan beneficiary numbers;
 - 10. Account numbers;
 - 11. Certificate/license numbers;
 - 12. Vehicle identifiers and serial numbers, including license plate numbers;
 - 13. Device identifiers and serial numbers;
 - 14. Web Universal Resource Locators (URLs);
 - 15. Internet Protocol (IP) address numbers;
 - 16. Biometric identifiers, including finger and voice prints;
 - 17. Full face photographic images and any comparable images; and

18. Any other unique identifying number, characteristic, or code, except as permitted for reidentification.³

C. If I assign a code or other means of record identification to allow de-identified information to be reidentified,

1. The code or other means of record identification is not derived from or related to information about the individual and is not otherwise capable of being translated so as to identify the individual, and
2. I will not use or disclose the code or other means of record identification for any purpose other than re-identification, and I will not disclose the mechanism for re-identification.

D. Before I allow a code to be used to re-identify this information,

1. If the purpose of the re-identification is within the scope of the original protocol, I will obtain approval of an amendment from the IRB and comply with the requirements of HIPAA; or
2. If the purpose of the re-identification is outside the scope of the original protocol, I will submit a full New Study Application, obtain IRB approval, and comply with the requirements of HIPAA.

Investigator's
signature:

David K. Mascarello

Date:

8/11/03

Investigator's position: Assistant Professor, Coriell Institute for Medical Research
If PI is a resident or fellow, a faculty advisor's signature is required.

• If required:

Faculty Advisor's signature: _____

Date:

Faculty Advisor's name: _____

³ If your research involves an unusual disease or condition, attach a statement explaining 1) the incidence of the disease or condition and 2) the potential of the information in your study to be used to identify the individuals.

• If required: Faculty Advisor's signature: _____ Faculty Advisor's name: _____	Date: _____
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For IRB Use Only

DECLARATION OF DE-IDENTIFICATION (HIPAA)
For Research by Cooper Employees and Medical Staff and/or within CHS
Institutional Review Board

The attached Declaration of De-identification has been reviewed and approved. The IRB finds that there is no reasonable basis to believe that the health information used in this study can be used to identify an individual, and therefore is not individually identifiable health information, based on satisfaction of the following requirements:

- ☒ Regulatory de-identification (45 CFR 164.514(b)(2)); or
☐ De-identification shown by statistical analysis, (45 CFR 164.514(b)(1)).

It was reviewed by the following process:

- ☐ Full Board Review; Date: _____
☒ Expedited Review by experienced, designated Board member; Date: 9/9/03
☐ Expedited Review by IRB Chair; Date: _____

Date Approved: 9/9/03
 Reviewer: Sheresa A. Spiegel