

DEPARTMENT OF DEFENSE  
U.S. ARMY MEDICAL RESEARCH AND MATERIEL COMMAND  
CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS

2004 PROSTATE CANCER RESEARCH PROGRAM

PEER REVIEW PANEL SUMMARY STATEMENT  
(PRIVILEGED COMMUNICATION)

Proposal Number: PC040924  
Proposal Category: Postdoctoral Traineeship Award  
Review Panel: Endocrinology  
Meeting Dates: 04/18/2004 - 04/20/2004  
Principal Investigator:  
Institution: California, University of, Los Angeles  
Project Title: Deciphering Contributions of (Beta)-Catenin to Androgen Independent Prostate Cancer by Modulation of PI3K Signaling  
Score: 1.1  
Standard Deviation: 0.25  
Adjectival Score: Outstanding (Range: 1.0 - 1.5)  
Budget Requested: \$125,000.00  
Duration Requested: 2.0 years

**SUMMARY:**

This proposal for a Postdoctoral Traineeship Award will enable the applicant to continue his studies and receive additional training conducive to advancing his career in prostate cancer research. The goal is to conduct studies deciphering the contributions of  $\beta$ -catenin to androgen independent prostate cancer by modulation of phosphatidylinositol-3-kinase (PI3K) signaling. The applicant will enroll in a postdoctoral program mentored by Dr. [REDACTED], an associate professor and the Howard Hughes Medical Institute and is Assistant Investigator at the University of California, Los Angeles (UCLA). The applicant expects to complete his Ph.D. studies in prostate cancer at the Prostate Centre, Jack Bell Research, at Vancouver General Hospital in 2004 with graduate training in cell biology. The training plan consists of weekly laboratory meetings, journal clubs, data presentations, and meetings with other researchers and trainees. The strengths of this proposal are many. The training plan is well designed and considered outstanding. The training environment at the UCLA Cancer Center is rich, with many prostate cancer researchers and trainees with whom to interact and is noted for a strong commitment to developing and analyzing new preclinical models for the study of prostate cancer in transgenic mice. The applicant is deemed to be outstanding in terms of past training and research directions, has been very productive early in his career, and has received numerous awards. He has demonstrated a comprehensive understanding of a complex regulatory system and has shown consistent commitment to understanding prostate carcinogenesis. The mentor is strong and has extensive experience in training medical and basic science research fellows who later receive academic appointments. There are no significant weaknesses. Overall the panel

rated this proposal **Outstanding** in all areas. The panel reviewed the proposal on the basis of the published evaluation criteria and rated it as described below.

**Evaluation Criteria Rating Scale 1 (low merit) to 10 (high merit):**

Criteria Description	Score
Applicant	9.9
Mentor	9.9
Training and Environment	9.8
Relevance	9.4
Research Strategy	9.5

**EVALUATION CRITERIA:**

**Applicant:**

Reviewer A: The applicant, \_\_\_\_\_, received a B.Sc. and M.Sc. in cell biology from the University of British Columbia, Canada, in 1995 and 1999 respectively. He is a Ph.D. candidate in prostate cancer at The Prostate Centre, Jack Bell Research, Vancouver General Hospital, Canada. The degree is expected in 2004. The applicant's strengths are his impressive productivity and his comprehensive understanding of a complex regulatory system. He has shown consistent commitment to understanding prostate carcinogenesis. His graduate training has been outstanding and his decision to move into preclinical animal models speaks to his considerable depth of understanding of the most important questions.

Reviewer B: The applicant is in the process of completing his Ph.D. in the laboratory of Dr. \_\_\_\_\_ at The Prostate Centre at Vancouver General Hospital. He has an impressive research and publication record in prostate cancer as evidenced by his high-quality papers (corresponding author) in *JBC* and *Oncogene*. His goals at UCLA are to obtain further training in prostate cancer using recently developed animal models and to eventually obtain a faculty position in prostate cancer research. Three letters of recommendation, from his future mentor, Dr. \_\_\_\_\_ from his current mentor, Dr. \_\_\_\_\_, and from Dr. \_\_\_\_\_, are all extremely favorable as to the applicant's potential as a postdoctoral fellow in prostate cancer research. He is considered a top candidate with outstanding abilities for critical thinking, independence, perseverance, originality, and research.

It is usually recommended that the research topic should be different from the Ph.D. topic. However, Mr. \_\_\_\_\_ is committed to continue prostate cancer research using mouse models to complement work in cell lines.

**Mentor:**

Reviewer A: The mentor, \_\_\_\_\_, received an M.D. from Beijing Medical College, China (1983), and a Ph.D. in molecular biology and genetics from Harvard Medical School, Boston, MA (1991), and did postdoctoral work at the Whitehead Institute, MIT, Cambridge, MA, from 1991 to 1996 in cell biology. Dr. \_\_\_\_\_ is an outstanding scientist who has developed some very exciting models of prostate cancer. She is a member of the UCLA Cancer Center and is Co-Principal Investigator (PI) for the UCLA center that is part of the National Cancer Institute's Mouse Models for Human Cancer Consortium. She is currently an associate professor, Department of Molecular and Medical Pharmacology, and assistant investigator, Howard Hughes Medical Institute, UCLA. Dr. \_\_\_\_\_ has an impressive record of mentoring young scientists at a number of different stages of their careers. The only concern is the amount of time that Dr. \_\_\_\_\_ will have available to devote to the applicant, but that is invariably an issue in productive laboratories. The applicant's ideas are very advanced and he will likely need only general guidance and support.

Reviewer B: Dr. \_\_\_\_\_ is an associate professor in the Department of Molecular and Medical Pharmacology and assistant investigator, Howard Hughes Medical Institute, UCLA. She has been instrumental in developing a more naturally derived model of prostate cancer in mice using prostate specific deletion of the phosphatase and tensin homologue (PTEN) gene. Dr. \_\_\_\_\_ is currently mentoring seven postdoctoral fellows, two medical fellows, three graduate students, and has demonstrated the ability to mentor postdoctorates for academic positions. A minor concern is that the large number of people she is supervising may lessen Dr. \_\_\_\_\_ attention to Mr. \_\_\_\_\_.

**Training and Environment:**

Reviewer A: The training environment is outstanding. Dr. \_\_\_\_\_ is associated with a very large, very active group of prostate cancer researchers. There is a well-developed training program in place, which includes a regular schedule of formal and informal interactions among the trainees, and numerous investigators in the prostate cancer group. The most significant strength of the environment is a very strong commitment to development and analysis of new preclinical models for studying prostate cancer in transgenic mice. It is difficult to imagine how this environment or the training program could be improved.

Reviewer B: The prostate cancer research environment at UCLA is one of the best in the world. There is a large core of well-known and dedicated prostate cancer research scientists at UCLA, with evidence of frequent journal and data clubs, and scientific meetings. The training at UCLA should further Mr. \_\_\_\_\_'s goal of obtaining a faculty position in prostate cancer research.

Consumer Reviewer: This applicant will have an excellent opportunity to thrive in the environment of the UCLA Cancer Center. He will be supervised by a well-known scientist in the field of prostate cancer biology and will be able to collaborate with a host of fellow scientists, including Dr. \_\_\_\_\_. The applicant will have the opportunity to participate in weekly laboratory meetings, as well as presenting his own research projects once a year in a campus-wide research seminar. He states that his goal is to become a faculty member at a

Prostate Cancer Research Center and the proposed program should allow him to achieve this goal.

**Relevance:**

Reviewer A: This proposal is highly relevant. The role of  $\beta$ -catenin in androgen regulation is an emerging field that, to date, has been based almost exclusively on analysis of cell lines in culture. Extension of this hypothesis into animal models is very likely to yield exciting new insight into prostate carcinogenesis.

Limited attention has been given to how the results of these studies may be translated into clinical practice. However, this is a training proposal and inclusion of studies beyond the animal models could result in lack of focus.

Reviewer B: Loss of PTEN occurs in 50 percent of advanced prostate cancer and the study of the consequences of this event in the development of androgen-independent prostate cancer is very relevant. Further studying the reason why 20 percent of high-grade prostatic intraepithelial neoplasia (PIN) contains nuclear  $\beta$ -catenin but only 5 percent contain activating mutations suggests additional pathways are at work. The study of carboxyl terminal modulator protein (CTMP) as an Akt inhibitor in prostate cancer is novel and may provide important data that complements PTEN.

Consumer Reviewer: Based on the facility where the applicant will be working, the mentor that will be supervising his work, and the fact that this line of research has been done before, it appears likely that the applicant will accomplish a successful result of clinical relevancy in the control and treatment of androgen-independent prostate cancer. Investigation of the signaling pathway of PI3K and showing that abrogation of that oncoprotein can reduce androgen receptor transcription appears to be very significant.

**Research Strategy:**

Reviewer A: The strengths of this proposal are abundant. The hypotheses are sound and well developed. The area of research is very important. The models are outstanding and the decision to focus on transgenic models of prostate cancer is a major strength. The experiments are well designed and certain to lead to important new observations. Completion of this training period will undoubtedly place Mr. [redacted] in a very favorable position to establish and develop an independent research program in prostate cancer.

The research plan is ambitious, but there is little doubt that the applicant will be able to complete the studies.

Reviewer B: Unlike the T antigen-driven TRAMP model, the prostate specific PTEN<sup>-/-</sup> mouse appears to be a more natural model of prostate cancer. These mice and the laser capture microdissection technique are powerful resources to evaluate the effect of PTEN loss on mutations/nuclear localization of  $\beta$ -catenin and other molecular events associated with activation of the PI3K pathway. The potential for obtaining PTEN<sup>-/-</sup> mice crossed with mice harboring activating mutations for  $\beta$ -catenin should further enhance this project. PTEN- and

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CTMP-inducible LNCaP cells are correctly proposed to elucidate, in a more controlled manner, these events *in vitro* and *in vivo* using castrated mice.

Objective 4 is not well developed and makes this proposal ambitious. Its methods could have been better described.

**Budget:**

The budget as requested is appropriate in amount and duration. Final budget is subject to Programmatic Review and negotiations.