

BIOGRAPHICAL SKETCH

NAME Dean John Bacich		POSITION TITLE Assistant Professor of Urology	
eRA COMMONS USER NAME DEANBACICH			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
University of Adelaide, Adelaide, Australia	B.Sc.	1986-1989	Biochemistry/Genetics
University of Adelaide, Adelaide, Australia	B.Sc (Hons.)	1990	Obstetrics and Gynaecology
University of Adelaide, Adelaide, Australia	Ph.D.	1991-1997	Medicine
Sloan-Kettering Institute for Cancer Research, New York, NY	Postdoctoral Fellow	1996-1999	Urology
Sloan-Kettering Institute for Cancer Research, New York, NY	Research Associate	1999-1999	Urology
The Cleveland Clinic Foundation, Cleveland, OH	Research Associate	1999-2002	Cancer Biology

RESEARCH AND PROFESSIONAL EXPERIENCE:**A. Personal Statement**

For the last 15 years my research has focused on prostate cancer, specifically the prostate cancer antigen, Prostate Specific Membrane Antigen (PSMA), which is a unique folate hydrolase that is highly expressed in prostate cancer. I have developed various mouse models to examine the biological role of PSMA in prostate cancer development. Additionally I have been examining the role that folate and PSMA has on the modulation of prostate cancer.

B. Positions and Honors. List in chronological order previous positions, concluding with your present position. List any honors. Include present membership on any Federal Government public advisory committee.

Professional Experience:

1996-1999 Postdoctoral Fellow, Department of Surgery, Division of Urology, Sloan-Kettering Institute for Cancer Research, New York, NY

1999-1999 Research Associate, Department of Urology, Sloan-Kettering Institute for Cancer Research, New York, NY

1999-2002 Research Associate, Department of Cancer Biology, Lerner Research Institute, The Cleveland Clinic Foundation, Cleveland, OH

2003-2005 Research Assistant Professor, Department of Urology, University of Pittsburgh School of Medicine, Pittsburgh, PA

2005-Present Assistant Professor, Department of Urology, University of Pittsburgh School of Medicine, Pittsburgh, PA

Honors and Awards:

1990 Department of Obstetrics and Gynaecology Honors Scholarship Awarded by the Department of Obstetrics and Gynaecology, The Queen Elizabeth Hospital, the University of Adelaide.

1991-1995 The University of Adelaide Reproductive Medicine Postgraduate Scholarship.
The Queen Elizabeth Hospital Research Foundation Supplementary Scholarship.

1992 Runner up: The Australian Society for Medical Research (South Australian division) Junior Scientist Award. Finalist: Australian Society for Reproductive Biology Junior Scientist Award.

- 1993 Finalist: Endocrine Society of Australia Junior Scientist Award.
Winner: The Queen Elizabeth Hospital Junior Scientist Award (In Training).
- 1995 Finalist: Endocrine Society of Australia Junior Scientist Award.
- 2000-2002 Yamanouchi Postdoctoral Fellow, awarded by the American Foundation for Urologic Disease. Proposal entitled "Generation of Animal Models for Prostate Carcinogenesis and Development Utilizing Prostate-Specific Membrane Antigen, a Unique Folate Hydrolase." (\$46,000 total award).

C. Selected peer-reviewed publications

Selected Publications most relevant to the current application

Yao, V., Berkman, CE, Choi JK, O'Keefe, DS* and **Bacich, DJ*** (2010). Expression of Prostate-Specific Membrane Antigen (PSMA), increases cell folate uptake and proliferation and suggests a novel role for PSMA in the uptake of the non-polyglutamated folate, folic acid. * these authors contributed equally to this manuscript. *Prostate* **70**(3) 305-16. PMID 19830782.

Yao, V., Parwani, A., Maier, C., Heston, WDW., **Bacich, DJ** (2008) Moderate Expression of Prostate Specific Membrane Antigen, a Tissue Differentiation Antigen and Folate Hydrolase, Facilitates Prostate Carcinogenesis. *Cancer Research* **68**(21):9070-7. PMID 133339

Yao, V and **Bacich DJ**. (2006) Prostate Specific Membrane Antigen (PSMA) expression gives prostate cancer cells a growth advantage in a physiologically relevant folate environment *in vitro*. *Prostate* 66:867-875

Bacich D.J., Wozniak, K., Lu, M., O'Keefe, D. S. , Callizot, N., Heston, W.D.W. and Slusher, B.S. (2005) Mice lacking Glutamate Carboxypeptidase II are protected from peripheral neuropathy and ischemic brain injury. *J Neurochem*. 2005 Oct;95(2):314-23.

Gregor PD, Wolchok JD, Turaga V, Latouche JB, Sadelain M, **Bacich D**, Heston WD, Houghton AN, Scher HI (2005) Induction of autoantibodies to syngeneic prostate-specific membrane antigen by xenogeneic vaccination. *Int. J Cancer* 116:415-21

O'Keefe DS, **Bacich DJ**, Heston WD. (2004) Comparative analysis of prostate-specific membrane antigen (PSMA) versus a prostate-specific membrane antigen-like gene. *Prostate* 58:200-10

Balaji KC, Rao PS, Smith DJ, Louis S, Smith LM, Sherman S, **Bacich DJ**, O'Keefe D. (2004) Microarray analysis of differential gene expression in androgen independent prostate cancer using a metastatic human prostate cancer cell line model. *Urologic Oncology* **22**:313-320.

Bacich, DJ, Ramadam, E, O'Keefe, DS, Bukhari, N, Wegorzewska, E, Ojeifo, O, Wrenn, CC, Bzdega, T, Wroblewska, B, Heston, WDW, Neale JH. (2002) Deletion of the Glutamate Carboxypeptidase II Gene in Mice reveals a second enzyme activity that hydrolyzes N-Acetylaspartylglutamate. *J. Neurochem*. 83:20-29

Bacich DJ, Pinto JT, Tong W, Heston WDW. (2001) Cloning, Expression, Genomic Localization and Enzymatic activities of the murine homologue of Prostate-Specific Membrane Antigen / NAALADase / Folh1. *Mam. Genome* 12 117-123

Uchida, A, O'Keefe, DS, **Bacich, DJ**, Molloy, PL, Heston, WDW. (2001) *In Vivo* Suicide Gene Therapy Model Using a Newly Discovered Prostate-Specific Membrane Antigen (PSMA) Promoter/Enhancer: A Potential Alternative Approach to Androgen Deprivation Therapy. *Urology* **58**:132-139

O'Keefe, DS, Uchida, A, **Bacich, DJ**, Watt, FB, Martorana, A, Molloy PL, Heston, WDW. (2000) Prostate-Specific Suicide Gene Therapy using the Prostate-Specific Membrane Antigen Promoter and Enhancer. *The Prostate* **45**:149-157

Gong MC, Chang, SS, Watt, F, O'Keefe, D.S., **Bacich, DJ**, Uchida, A., Bander, NH., Reuter, VE., Gaudin, PB., Molloy, PL., Sadelain, M. and Heston, W.D.W. (2000) An Overview of Evolving Strategies Incorporating Prostate-Specific Membrane Antigen (PSMA) as a Target for Therapy. *Molecular Urology* **4**(3):217-222

Pinto JT, Qiao C, Xing J, Suffoletto BP, Schubert KB, Rivlin RS, Huryk RF, **Bacich DJ**, Heston WDW. (2000) Alterations of Prostate Biomarker Expression and Testosterone Utilization in Human LNCaP Prostatic Carcinoma Cells by Garlic derived S-Allylmercaptocysteine. *The Prostate* **45**:304-314

Chang SS, O'Keefe DS, **Bacich DJ**, Heston WDW, Reuter VE, Gaudin PB (1999) Prostate-Specific Membrane Antigen (PSMA) is produced in tumor-associated neovasculature *Clinical Cancer Research*, **5**(10):2674-81.

Kaplinsky RS, **Bacich DJ**, O'Keefe DS, Rabbani F, Tomassi MJ, Huryk R, Bastar AL, Miller WH, Heston WDW and Fair WR (1998) Neither PSMA RT-PCR nor MTHFR genotype predicts PSA failure after prostatectomy. *Molecular Urology* **2**:221-227

D. Research Support

Active Support:

Folate and PSMA Interact to Regulate DNA Methylation and Prostate Carcinogenesis

Co-Principal Investigator: Dean Bacich, Ph.D.

Agency: NCI/NIH **Type:** Multi-PI RO1 **Period:** 4/1/10-3/31/15

Specific aims: (1) Determine if (a) PSMA expression regulates intracellular folate levels, and (b) if folate levels regulate DNA methylation in prostate tissues, (2) Ascertain if low levels of available folates increase the invasive capacity of PSMA and lead to genomic hypomethylation and DNA instability, and subsequently carcinogenesis, and (3) Establish if, prior to initiation of prostate carcinogenesis, folate supplementation is protective; and if following initiation, excess folate supplementation promotes prostate tumor growth and progression. We will determine if PSMA mediates enhanced uptake of systemic folate in the prostate under these circumstances, and if there is consequent altered epigenetic programming of tumor suppressor genes.

“FOLATE/PSMA REGULATION OF PROSTATE CANCER PROGRESSION.”

Principle Investigator: Dean Bacich, Ph.D.

Agency: DOD **Period:** 3/15/07-3/14/10 (1 year no cost extension requested)

Specific Aims: The specific Aims are (1) to determine the role of dietary folate on prostate cancer growth and progression by (A) comparing the effect of low, standard and high folate diets on tissues recombinants, utilizing PSMA transgenic mouse prostate epithelial cells and Rat Urogenital Mesenchyme (rUGM) cells grown underneath the kidney capsule of Nude mice during the promotion phase of this mode; (B) examining if folate levels modulate the effects of the folate hydrolase PSMA during prostate cancer invasion, and (C) we will compare serum and red blood cell folate levels of prostate cancer patients at surgery to expression levels of PSMA in both their prostate tumor and normal prostate tissue adjacent to tumor. Other specific aims included (2) to determine the efficiency of inhibitors to folate hydrolase in preventing prostate cancer growth and progression in a PSMA transgenic mouse tissue recombinant model of prostate cancer, and (3) to determine the efficiency

of inhibitors to folate hydrolase in a human prostate cancer tissue recombinant xenograft model of prostate cancer growth and progression.

Completed Research Support

“Prostate Specific-Membrane Antigen (PSMA) Inhibitor Therapy for the Prevention of PSMA Induced Prostate Cancer”

Principal Investigator: Dean Bacich, Ph.D.

Agency: Pittsburgh Foundation **Period:** 8/1/06-4/31/09

Specific aims: We will examine the effect of specific inhibitors to the enzymatic activity of PSMA on 1) our PSMA based mouse model of prostate cancer and 2) a human prostate cancer tissue recombinant model. This therapy will address both prostate cancer progression and initiation.

Title: Dietary folate manipulation to prevent prostate cancer progression

Principal Investigator : Denise O’Keefe, Ph.D

Agency: American Institute for Cancer Research

Performance Period: July 2007 – June 2009 (Six month no cost extension requested)

Specific Aims: We hypothesize that dietary folate levels could be used to alter the progression of pre-neoplastic foci in men “at risk” for developing prostate cancer as well as the progression of tumors in men with disease by modulation of epigenetic mechanisms. We will test this through two specific aims. **1:** To determine if patients “at risk” for developing prostate cancer should increase folic acid intake to decrease their risk. **2:** To determine if patients who already have prostate cancer will benefit from either an increase or decrease in folic acid intake as compared with basal levels. For both aims, we will use a novel human tissue recombinant model.

“Disruption of the Epigenome by Extremes of Dietary Folates”

Principal Investigator: Denise O’Keefe, Ph.D.

Agency: NIH **Type:** PA-04-099 R21 **Period:** 9/1/07-8/30/09 (1 year no cost extension)

Specific aims: The specific aims are 1) To examine global and specific epigenetic changes in primary human prostate tissue (from cancer, normal tissue adjacent to cancer, and cancer-free donors) under different conditions of dietary folate (low, normal, high when grown in mouse. 2) To determine if the folate regulating enzyme PSMA mediates epigenetic changes when it induces invasive lesions in a transgenic tissue recombinant model and 3) To study the mechanism by which low extracellular folic acid levels result in epigenetic silencing of the ABCG2 gene.

“The Role of Prostate-Specific Membrane Antigen (PSMA) in Prostate Cancer Initiation and Progression:”

Principal Investigator: Dean J. Bacich, Ph.D.

Agency: US Army **Period:** 11/1/04 – 11/30/07 **Type:** W81XWH 05 1 15

The goal of this proposal is to determine the basic biology of PSMA in prostate cancer. The primary experimental approach is to create tissue recombinants from transgenic prostate gland engineered to express human PSMA, and implant them under the kidney capsule in immunoincompetent mice. The ability of these tissues recombinants to mimic the progression of prostate cancer will be studied immunohistologically, biochemically and via gene expression analysis.