Award Number: W81XWH-11-1-0367

TITLE: Analysis of Novel Prostate Cancer Biomarkers and their Predictive Utility in an Active Surveillance Protocol

PRINCIPAL INVESTIGATOR: Adam S. Feldman, M.D., M.P.H.

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

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Analysis of Novel Prostate Cancer Biomarkers and their Predictive Utility in an Active Surveillance Protocol

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The Research Project supported by this DOD PCRP Physician Research Training Award investigates novel biomarkers for prostate cancer detection and the investigation of biomarkers in active surveillance. This report summarizes the research and accomplishments in the fourth year of this award. In this year, I have had continued success in investigating potential proteomic prostate cancer biomarkers. In addition, we have begun to investigate metabolomic signatures in prostate cancer in urine and tissue. I also have continued my clinical investigation of men with prostate cancer on active surveillance. We published a manuscript on our cohort series and have presented at national meetings our updated investigations on young men on active surveillance for low risk prostate cancer.

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**Introduction:**

The Research Project supported by this DOD PCRP Physician Research Training Award investigates novel biomarkers for prostate cancer detection and the investigation of biomarkers in active surveillance. The goals and objectives of this study are summarized by the Specific Aims: 1. Evaluate the relative levels of expression of our panel of candidate protein biomarkers in urine, tissue and serum from patients with prostate cancer compared with normal controls to identify prostate cancer specific biomarkers. 2. Evaluate the relative urine, tissue and serum levels of these prostate cancer specific biomarkers within our entire active surveillance (AS) cohort to identify accurate biomarkers predictive of indolent vs. progressive prostate cancer. The funding from this Physician Research Training Award provides salary support for Dr. Adam S. Feldman to secure protected time as a translational and clinical investigator in prostate cancer research. It also provides salary support for a Research Assistant for this research.

**Body:**

The first year of my DOD PCRP PRTA was very productive from both a translational laboratory and clinical research standpoint. In summation, I used mass spectrometry (MS) to quantitatively compare the entire urinary proteome and identify differentially expressed proteins in the urine from men with prostate cancer as compared with those found in controls. The MS analysis identified >1400 unique proteins, comparative analysis revealed 55 potential prostate cancer specific proteins, and using bioinformatic database analyses, we narrowed this list to 20 biologically relevant proteins. Using semi-quantitative Western blot, we investigated several proteins on the list of 20 relevant proteins including Leukocyte Elastase Inhibitor, Annexin A1, Plastin-2, Vimentin, and Tissue Inhibitor of Matrix Metalloproteinase Type 1 (TIMP-1). We used urine specimens of 56 men, both from PrCA and Controls. These urine specimens were selected from our urine biospecimen bank, prospectively obtained and developed from our urologic oncology clinic at Massachusetts General Hospital. In TIMP-1, we found a significant difference in TIMP-1 expression between men with Gleason 3+3 disease and men with Gleason 7 or greater.

In the second year of my DOD PCRP PRTA, I further explored the compelling data from the TIMP-1 Western blots and returned to my original list of 55 differentially expressed potential prostate cancer specific proteins to assess other possible candidate markers. Looking at TIMP-1, we used Enzyme-Linked Immunosorbent Assays (ELISA) and Immunohistochemistry (IHC) to corroborate the data we found in Western blot analyses. Using IHC, we were able to show increased staining for Gleason 8 or higher, compared to lower Gleason scores supporting our previous Western blot data and further pointing to the potential of TIMP-1 as a relevant biomarker for prostate cancer. For ELISA analysis of TIMP-1 expression we used the same cohort of 56 men, both PrCA and Controls, as analyzed by Western blot. Although we demonstrated differential expression across our cohort, we were unable to effectively reproduce the results we found in Western blot. This discrepancy between Western blot and ELISA results were consistent across two separate commercially available ELISA kits (R&D Systems, Mineapolis, MN and EMD Millipore, Billerica, MA), suggesting that possibly the Western blot antibodies and
ELISA antibodies were measuring separate epitopes and therefore demonstrating different results. In my second year we also returned to my original list of 55 differentially expressed potential prostate cancer specific proteins, using both Western blot and ELISA analyses with several representative specimens as an initial evaluation to screen for those proteins with potential clinical relevance.

In the third year of my DOD PCRP PRTA, I pursued the promising Western blot candidates from year two, including Semenogelin-2, Lactoylglutathione Lyase, Hepsin, Alpha-1-Antichymotrypsin (Serpina3), and Growth-Inhibiting Protein 12 (GIP 12). We also investigated the protein candidates Prohibitin, Radixin, Taldo1, Fructose-Bisphosphate Aldolase A, Lactate Dehydrogenase A, CD63, Cytochrome C, Ras-related protein RAB-3A, Macrophage Capping Protein, 10kd Heat Shock Protein, Annexin A3, Sorbitol Dehydrogenase, Fibrinogen Beta Chain Precursor, and Creatine Kinase B-Type. We further investigated other biologically relevant candidates including Annexin A1, Cystatin B, and AZI. These additional protein candidate markers unfortunately did not demonstrate promising results by extensive Western Blot evaluation. We also pursued ELISA analysis of biologically relevant and promising candidates Prohibitin, 10kd Heat Shock Protein, and Growth-Inhibiting Protein 12 (GIP 12), however, did not identify clear differences in expression between clinical disease states. One protein, however, that continued to show promise, in addition to TIMP-1, was Semenogelin II. Semenogelin II is a protein that normally participates in the formation of the seminal coagulum. A handful of publications in the literature have suggested involvement of the semenogelin proteins in prostate cancer.

In this past fourth year of my DOD PCRP PRTA, I have continued to further investigate potential proteins as urinary biomarkers for prostate cancer. I further analyzed the viability of Semenogelin II as a potential prostate cancer biomarker, as we had promising preliminary data by Western Blot analysis in year three. To investigate this marker we used urine specimens of 54 men, both from men with PrCa and biopsy negative controls. These urine specimens were selected from our urine biospecimen bank, prospectively obtained and developed from our urologic oncology clinic at Massachusetts General Hospital. We tested two commercially available antibodies for Western Blot of Semenogelin II (Santa Cruz Biotechnology, Inc. and Sigma Aldrich) and optimized our Western blot protocol for the Santa Cruz antibody for more accurate characterization of expression.

Figure 1 shows a representative Western Blot demonstrating the expression of Semenogelin II in protein isolated from urine specimens obtained from men with prostate cancer and normal controls. This image suggests that while there is differential
expression observed between patients, there is no clear trend between control and cancer, or within cancer grades. Our overall analysis of Western blot expression data confirmed that while we saw variable expression among patients, we unfortunately found no clear definable trend. Figure 2 demonstrates the Western blot results for all 54 patients. This

Figure 2: Scatter plot (A) and individual patient column chart (B) illustrating semi-quantitative Western blot analysis of urinary expression of Semenogelin II (65kd) in 54 patients: 16 controls, 15 Gleason 3+3, 16 Gleason 4+3, 7 Gleason 8-9.
cohort included 16 biopsy negative controls, 15 men with Gleason 3+3, 16 men with Gleason 4+3, and 7 men with Gleason 8-9. The median expression values for Gleason 6/7 and Gleason ≥8 disease were 0.27 (IQR 0.20-0.52) and 0.29 (IQR 0.22-0.979), respectively.

To further investigate the expression of Semenogelin II in urine, we performed ELISA

Figure 3: Scatter plot (A) and individual patient column chart (B) illustrating quantitative ELISA of urinary expression of Semenogelin II in 33 patients: 9 controls, 9 Gleason 6, 9 Gleason 7, 6 Gleason 8-9.
Concerned (Wuhan USCN Business Co., Ltd.) on the urinary protein isolate. Interestingly, we saw more of a trend in expression, with lower expression in high grade cancers (Gleason 8-9) as compared to Gleason 6 and 7 prostate cancer specimens (Figure 3). Although this relationship bordered on statistical significance with a p value of 0.053, it is likely underpowered to demonstrate this relationship. Interestingly, this observed trend of reduced expression in higher risk disease may be supported in the published literature on Semenogelin in prostate cancer. Izumi, et al.¹ investigated the expression of Semenogelin I and II in prostate cancer tissues and identified that although there was an increased intranuclear expression of these proteins in prostate cancer, there was also a decreased secretion of these proteins in prostate cancer. Canacci, et al.² demonstrated a reduction in Semenogelin II expression in Gleason 8 and higher tumors compared with lower grades, and also found that Semenogelin II-negative tumors had a greater risk of biochemical recurrence after radical prostatectomy. We are currently expanding our own investigation of this relationship and are comparing these expression profiles with the clinical outcomes of these patients over time.

In addition to our work with Semenogelin II, given our prior Western blot results and biological plausibility of Serpin B1 (Leukocyte Elastase Inhibitor), we pursued further investigation of this potential marker. Serpin B1 is a serine protease inhibitor in the

cytoplasm of polymorphonuclear neutrophils, acting on cathepsin G and proteinase-3, helping to protect the cell from damage at tissue inflammatory sites.

Similar to our evaluation of Semenogelin II described above, we investigated the urinary expression of Serpin B1 using Western blot analysis in 54 patients, including 16 biopsy negative controls, 15 men with Gleason 3+3, 16 men with Gleason 4+3, and 7 men with Gleason 8-9. Across all groups, we saw no clear trend in expression, as demonstrated in Figure 4A. The median expression values for Gleason 6/7 and Gleason ≥8 disease were 0.68 (IQR 0.22-1.16) and 0.50 (IQR 0.14-0.94), respectively. This difference, however, was not statistically significant as seen in Figure 4B. Figure 4C demonstrates individual patient expression levels of Serpin B1. Ashida, et al.3 have suggested that Serpin B1 expression may be reduced in prostate cancer compared with benign prostate tissue. We are continuing to investigate our cohort of men for expression of Serpin B1 in urine via ELISA.

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Figure 4: Scatter plot (A) and individual patient column chart (B) illustrating semi-quantitative Western blot of urinary expression of Serpin B1 (65kd) in 54 patients: 16 controls, 15 Gleason 3+3, 16 Gleason 4+3, 7 Gleason 8-9.
In addition to a proteomic investigation for novel biomarkers in prostate cancer, we have also begun to use metabolomics for urinary biomarker discovery. We build upon our experience in investigating metabolomic changes in prostate cancer and normal tissues in collaboration with Leo L. Chang, Ph.D., here at Massachusetts General Hospital. This is an NIH funded project in which we investigate the metabolomics profiles of prostate cancer tissue. Through this study we have investigated metabolomic signatures in prostatectomy specimens and prostate biopsies using \textit{ex vivo} MR spectroscopy. We have begun to utilize multiparametric prostate MRI and MRI-Ultrasound fusion biopsy of the prostate to investigate biopsy cores taken from MRI targetable lesions and uninvolved prostate regions that appear normal by imaging criteria. Figure 5 demonstrates metabolomic spectra of prostate cancer regions compared with non-malignant prostate tissue.

![Figure 5: Metabolomic spectra can be seen in the left panel from prostate cancer tissue (A) and non-malignant prostate tissue (B), obtained from the same patient.](image)

We have now begun collecting voided urine specimens for metabolomic profiling in men undergoing prostate biopsy who enroll in our prostate cancer metabolomics study. In addition to assessing their biopsy cores in the described \textit{ex vivo} manner using MR spectroscopy, we also assess the paired urine specimens using nuclear magnetic resonance (NMR). Thus far we have collected such matched specimens from eight patients at the time of MRI-Ultrasound fusion biopsy of the prostate. Examples of spectra obtained from urine and matched biopsy core samples from a patient with prostate cancer are presented in Figure 6A, while its urine spectrum was compared with that of patient

![Figure 6: (A) Metabolomic spectra of urine and prostate cancer tissue from a patient found to have prostate cancer on biopsy. (B) Metabolomic spectra of urine from patients with and without prostate cancer. (C) Comparisons of urine spectral intensity at 4.04ppm from patients with and without prostate cancer.](image)
with a benign fusion biopsy result (Figure 6B). Comparisons of urine spectra from patients with prostate cancer and benign biopsies revealed a significant difference in the spectral intensity for the resonance at 4.04ppm, according to the Mann-Whitney-Wilcoxon (t-test for non-normal distributed samples) Test (Figure 6C). Identification of the resonance and verification with additional patients are underway with this ongoing project.

In addition to our laboratory work, we continued to build on our previous work in further developing our clinical database and evaluating our cohort of men on active surveillance (AS) for low risk prostate cancer. Our database now consists of 992 men on active surveillance for low risk prostate cancer identified through billing and pathology records. We are continuing to update this database and investigate clinical outcomes in this cohort.

Although AS had been practiced throughout this entire period, in 2008 our group agreed upon formal guidelines for AS at our institution. Inclusion guidelines included Gleason ≤ 6, Gleason 7 in select patients with low volume, no more than 3/12 cores positive with ≤20% in each core, and PSA <10. Our AS follow-up protocol involves PSA testing and a digital rectal examination every four months for one year, followed by every six months for two years, and then annually. Those on AS also have a mandatory repeat 12-core biopsy 6-12 months after initial diagnosis, although we have recently been increasing the utilization of multiparametric prostate MRI and MR-ultrasound Fusion prostate biopsy when a targetable lesion is found. Additional biopsies after the first confirmatory biopsy are at the discretion of the treating physician.

In this past year we have published our manuscript on 469 men within our AS cohort in the journal, Urologic Oncology. The results of this work were included in my previous annual report last year. We have continued to investigate this growing cohort and more recently have investigated the outcomes of younger men who initiate active surveillance for low risk prostate cancer at the age of 60 years or less. This is a group of men on which there is a paucity of literature.

Our group of men who started active surveillance at 60 years or younger consists of 177 men, all of whom had Gleason 6 disease on their intial diagnostic biopsy. Median age was 55 years and 92.7% were clinical stage T1c. Baseline characteristics of the cohort are seen in Figure 7A and pathology on repeat biopsy is listed in Figure 7B. 28.8% progressed to treatment for the indications listed in Figure 7C. Interestingly, of those who went on to have surgery, 16.2% were found to have pT3 disease. Over a median follow up of 4.4 years, 20.6% (32/155) of men were ultimately upgraded on any subsequent biopsy or at the time of radical prostatectomy (RP), and 32.4 % (12/37) of men upgraded at time of RP compared to last pre-RP biopsy. This cohort demonstrates that AS is a reasonable option for carefully selected men under 60 with very low risk prostate cancer, however, patients must be surveyed closely and understand the risk of ultimately needing treatment.
In addition to significant research accomplishments, I continue to meet my goals within the training program of this grant. I meet regularly with my two mentors, Drs. Matthew Smith and Bruce Zetter. In our regular meetings, we not only discuss research progress, but also focus on career planning and guidance. I attend regular urologic oncology clinical and research conferences at our institution and both attend and present at regional and national scientific meetings. I attend regular laboratory research meetings both for our own research progress, as well as reviewing other associated research in the current literature. I also have participated multiple times as an invited reviewer of research grant applications for the Prostate Cancer Foundation Young Investigator Awards and Challenge Awards.

Figure 7: Baseline data and outcomes of men on active surveillance for low-risk prostate cancer, who started on active surveillance at the age of 60 or younger.
Key Research Accomplishments:

- Further analysis of potential proteomic urine based prostate cancer biomarkers, including Semenogelin II and Serpin B1.
- Initiation of investigation into urine based metabolomic signatures of prostate cancer detection and disease grade, as compared with the metabolomics profiles of patient matched prostate cancer tissue specimens.
- Continued development analysis of our large database of our cohort of men with low risk prostate cancer on active surveillance, including the publication of a manuscript and investigation of younger men on active surveillance.

Reportable Outcomes:


Conclusion:

In summary, these past four years of my DOD PCRP PRTA have been very productive. We thoroughly investigated our list of biologically relevant candidate prostate cancer biomarkers and have demonstrated promising results with TIMP-1, Semenogelin II and Serpin B1. We are continuing to investigate these markers in localized and metastatic disease are moving forward toward the development of a manuscript discussing the discovery and analysis of these markers.

Our new approach to include metabolomics profiling is also very exciting as a method for biomarker identification which takes a novel approach and integrates findings in tissue, in addition to urine.
In addition to success in our laboratory work, we have also made significant accomplishments in continued analysis of our large cohort of men on active surveillance for prostate cancer and continue to build this database and further assess multiple important clinical questions.

This described work is very relevant to current clinical practice in prostate cancer and meets any potential “so what” criteria. New diagnostic and predictive biomarkers with improved performance characteristics than prostate specific antigen (PSA) are sorely needed. The work funded by this grant directly addresses that challenge and we are already beginning to produce results toward that goal. In addition, it is clear that we have historically over-treated low risk prostate cancer. Active surveillance is a management strategy for low risk disease which will help ameliorate the problem of overtreatment. Our large database of men on active surveillance will help us to understand the safety, efficacy and outcomes of this strategy and will help us better select men for AS in the future. Biomarker analysis within this cohort will also help us better understand who truly has very low risk disease and can safely avoid radical treatment.

**Appendices:**
Curriculum Vitae for Dr. Adam S. Feldman is included in this annual reporting.
Date Prepared: June 18, 2015

Name: Adam S. Feldman, M.D., M.P.H.

Office Address:
Department of Urology
Massachusetts General Hospital
55 Fruit Street, GRB 1102
Boston, MA 02114 United States

Education
1994 B.A. - Biological Basis of Behavior
University of Pennsylvania

1996 M.A. (Alpha Epsilon Lambda) - Medical Sciences
Boston University School of Medicine

2000 M.D. (Alpha Omega Alpha)
University of Massachusetts Medical School

2009 M.P.H. – Clinical Effectiveness
Harvard School of Public Health

Postdoctoral Training
07/00-06/01 Intern in Surgery, Massachusetts General Hospital
07/01-06/02 Resident in Surgery, Massachusetts General Hospital
07/02-06/05 Resident in Urology, Massachusetts General Hospital
07/05-06/06 Chief Resident in Urology, Massachusetts General Hospital
07/06-06/08 Fellow in Urologic Oncology, Massachusetts General Hospital

Faculty Academic Appointments
2000-2006 Clinical Fellow in Surgery, Harvard Medical School, Boston, MA
2006-2010 Instructor in Surgery, Harvard Medical School, Boston, MA
2010-present Assistant Professor of Surgery, Harvard Medical School, Boston, MA

Appointments at Hospitals/Affiliated Institutions
2006-present Assistant in Urology, Massachusetts General Hospital, Boston, MA

Major Administrative Leadership Positions
2011 Scientific Program Chair, American Urological Association, New England and Mid-Atlantic Sections, Annual Meeting
Other Professional Positions
2012 Member: Scientific Program Committee, American Urological Association, New England Section Annual Meeting
2012-present Board Member: Sean Kimerling Testicular Cancer Foundation
2013-present Co-Leader of the Career Development Program: DFCI/HCC Prostate Cancer SPORE

Committee Service - Local
2012-present Member: Surgical Coordination Committee, Department of Urology, MGH
2013-present Member: MGH eCare Big Data and Data Repository Workgroup
2013-present Urology Representative: Clinical Research Workgroup of the Continuous of the Continuous Research Operations Improvement (CROI) Task Force

Committee Service - Regional
2012-present Member: Massachusetts Medical Society Committee on Men’s Health

Committee Service - National
2013-present Member: Eastern Cooperative Oncology Group (ECOG) Genitourinary Committee

Professional Societies
1998-present Massachusetts Medical Society, Member
2002-present American Urological Association, Member
2004-present American Association of Clinical Urologists, Member

Grant Review Activities
2012-13 Prostate Cancer Foundation Young Investigator Awards Review Committee
2013-15 Bladder Cancer Advocacy Network Young Investigator Awards Review Committee
2013-14 Prostate Cancer Foundation Challenge Awards Review Committee
2013 Prostate Cancer Foundation Young Investigator Awards Review Committee

Editorial Activities
2006 Ad-Hoc Reviewer, International Braz J Urol
2010-present Ad-Hoc Reviewer, Urology
2010-present Ad-Hoc Reviewer, Prostate Cancer and Prostatic Diseases
2010-present Ad-Hoc Reviewer, Urologic Oncology
2011-present Ad-Hoc Reviewer, BJU International
2012-present Ad-Hoc Reviewer, Molecular Cancer Research
2013-present Ad-Hoc Reviewer, European Urology

Editorial Board
2015-present Editorial Board Member, BMC Urology

Honors and Prizes
1996 Alpha Epsilon Lambda - Graduate Honors Society, Boston U. School Of Medicine
2000 Senior Scholar - Department of Surgery, U. Of Massachusetts Medical School
2000 Alpha Omega Alpha Honor Medical Society, U. Of Massachusetts Medical School
2003 Resident Abstract Travel Award, American Urological Association - New England Section
Report of Funded and Unfunded Projects

Funding Information

Past:

1997  Student  Institutional Grant, Joseph P. Healy Grant, Pre-clinical Intercultural Program, University of Massachusetts Medical School
   • Summer intercultural immersion program in clinical medicine in Latino community in Miami, FL

1997-1998  Project Director  Institutional Grant, Community Service Grant funding Creating Our Future Program, University of Massachusetts Medical School
   • Program in which medical students tutored and mentored children of homeless families in Worcester, MA

2007-2008  P.I.  Claire and John Bertucci Prostate Cancer Research Fund, A Proteomic Approach to Prostate Cancer Biomarker Discovery
   • Use proteomic techniques for urine biomarker discovery in men with prostate cancer

2007-2009  P.I.  Company – Predictive Biosciences; Evaluation of Urine Based Protein Biomarkers in Bladder Cancer
   • Analyze urinary proteins as novel diagnostic and surveillance markers in bladder cancer
   • Sponsored Research Agreement

2009-2010  P.I.  Claire and John Bertucci Prostate Cancer Research Fund - Active Surveillance for Prostate Cancer: Management Patterns, Outcomes, and Quality of Life
   • Funding supports research personnel for data mining and management

2008-2012  P.I.  Prostate Cancer Foundation – Young Investigator Award; Proteomic Discovery and Analysis of Novel Biomarkers in Prostate Cancer

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• Use proteomic mass spectrometry techniques for identification of novel prostate cancer biomarkers in urine and serum

2009-present Investigator
Harvard Catalyst Pilot Grant Program
NIH UL1 RR 025758-02 Clinical and Translational Science Center Grant
Sonoelastography for Tumor-Targeted Prostate Biopsy

• This study is a pilot study of the utility of sonoelastography for targeting biopsy to foci of cancer in the prostate.

Current:

2009-present Investigator
RTOG 0712: A Phase II Randomized Study for Patients With Muscle-Invasive Bladder Cancer Evaluating Transurethral Surgery and Concomitant Chemoradiation by Either BID Irradiation Plus 5-Fluorouracil and Cisplatin or QD Irradiation Plus Gemcitabine Followed by Selective Bladder Preservation and Gemcitabine/Cisplatin Adjuvant Chemotherapy

2011-present P.I.
Department of Defense Prostate Cancer Research Program - Physician Research Training Award; Analysis of Novel Prostate Cancer Biomarkers and Their Utility in an Active Surveillance Protocol

• The research project will investigate novel biomarkers in prostate cancer detection and prediction of disease outcome.

2013-present P.I.
Project Title: Validating Conditionally Reprogrammed Cells to Advance Personalized Medicine for Prostate Cancer
Role on the Project: Site PI
Supporting Agency: Georgetown University/DoD (W81XWH-12-PCRP)

2013-present P.I.
Project Title: A Collaborative Study Using Primary Prostate Cells and their Reprogramming for the Study of Progression to Castrate Resistant Prostate Cancer
Role on the Project: Site PI
Supporting Agency: Georgetown University/GHUCCTS/Clinical and Translational Science Awards

2013-present Investigator
RTOG0938: A Randomized Phase II Trial of Hypofractionated Radiotherapy for Favorable Risk Prostate Cancer

2013-present Investigator
Phase III randomized clinical trial of proton therapy vs IMRT for low or low-intermediate risk prostate cancer

2013-present Investigator
Characterizing Prostate Cancer by ex vivo MRS Signature (Cheng)
NIH/NCI, R01CA115746
The proposed project is aimed at permitting translation of our pre-clinical human study results into new diagnostic and evaluation paradigms for the PCa clinic.
Unfunded Projects

Past:

1991 Research Assistant
Isolation and sequencing of a conserved domain of the DnaJ family of chaperonins. Department of Surgical Research, Children’s Hospital, Boston, MA.

1994-1995 Research Assistant
Evaluation of Critical Pathways for CHF, DVT, and Normal Vaginal Delivery with 24 hour LOS. Brigham and Women's Hospital, Boston, MA.

1994-1995 Research Assistant
Adverse Drug Events Prevention Study Group. Brigham and Women's Hospital, Harvard School of Public Health.

1999-2000 Research Fellow
Characterization of Angiogenic Markers in the Rat Genitourinary System. Laboratory for Cellular Therapeutics and Tissue Engineering, Department of Urology, Children’s Hospital, Boston, MA.

2002-2004 Investigator
Development of bladder cancer in a murine model for Cables knock-out mice exposed to N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN). Laboratory of Urology/Pathology, Massachusetts General Hospital, Boston, MA.

2002-2004 Investigator
The Role of Cables, a novel cell-cycle regulatory protein in human transitional cell carcinoma and prostate cancer. Laboratory of Urology/Pathology, Massachusetts General Hospital, Boston, MA.

2004-2005 Investigator
Proteomic analysis of voided urine specimens for biomarker discovery and validation in prostate and bladder cancer. Laboratory of Urology/Pathology, Massachusetts General Hospital. Department of Vascular Biology, Children’s Hospital, Boston, MA.

2007-2008 Investigator
Laparoscopic and Open Radical prostatectomy after laparoscopic inguinal hernia repair. Massachusetts General Hospital, Boston, MA.

2010 Investigator
Outcomes of Organ Sparing Surgery in Penile Cancer. Massachusetts General Hospital, Boston, MA.

2010-2012 Investigator
Multi-Institutional Bladder Cancer Quality Care Initiative for non-metastatic muscle invasive transitional cell carcinoma of the bladder.

Current:

2006-present P.I.
A comparison of nephron sparing techniques: percutaneous radiofrequency ablation (RFA) vs. open and laparoscopic partial nephrectomy. Massachusetts General Hospital, Boston, MA.

2009-present P.I.
Active Surveillance in Prostate Cancer: Retrospective analysis of quality of life and outcomes and development of a prospective cohort. Massachusetts General Hospital, Boston, MA.

2010-present P.I.
Renal Biopsy for Small Renal Masses. Massachusetts General Hospital, Boston, MA.

2013-present Investigator
PARTIQoL (Prostate Advanced Radiation Technologies Investigating Quality of Life) Registry

Report of Local Teaching and Training

Teaching of Students in Courses

2006-present  Urologic Surgery

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2008-2010  Patient Doctor II
Attending 5 Medical Students 8 hours/year for 1 year(s) none reported

2010 HMS2 Pathophysiology contact time prep time

Attending 25 Medical Students 3 hours/year for 1 year(s) 3 hours

Formal Teaching of Residents, Clinical Fellows and Research Fellows (post-docs)

2007 Surgical Chief’s Rounds - Department of Surgery - Injuries to the Urogenital Tract

Lecturer 25 Residents contact time prep time

2007-present Ambulatory Teaching Rounds - Department of Medicine – Uro-oncology for the primary care physician; Management of Small Renal Masses

Lecturer 30 Residents contact time prep time

2010 General Surgery Teaching Rounds – Department of Surgery – Bladder Cancer Review

Lecturer 25 Residents contact time prep time

Clinical Supervisory and Training Responsibilities

2006-present Urological Surgery – Training of Residents/Fellows 15 hours/week

2008-present Sub-specialty Faculty Advisor for the Acute Care Surgery fellow 10 hours/year

Laboratory and Other Research Supervisory and Training Responsibilities

2007-present Supervision and mentoring of Research Fellow 5 hours/week

Formal Teaching of Peers (e.g., CME and other continuing education courses)

1996-1997 Worcester, MA Teaching Assistant/Tutor in Biochemistry, University of Massachusetts Medical School Responsibility: Tutor fellow medical students in Biochemistry.

2009 Las Vegas, NV Faculty (CME Course): Maximizing Bone Health for Patients With Prostate Cancer: Establishing the "Who, What, Why & How?"

2009 Scottsdale, AZ Faculty (CME Course): Maximizing Bone Health for Patients With Prostate Cancer: Establishing the "Who, What, Why & How?"

2010 San Francisco, CA Faculty (CME Course): Master Class on Integrating Novel Antiresorptive Agents into the treatment of Prostate Cancer

2010 Boston, MA Faculty (CME Course): Trauma and Critical Care Symposium – Penile and Genitalia Trauma

2011 Boston, MA Faculty (CME Course): Society of Translational Oncology Prostate Cancer Symposium – Prostate Cancer: Progress and Promise

2011 Cambridge, MA Faculty (CME Course): Primary Care Internal Medicine: Principles & Practice – Case Studies in Urology [Invited Lecture]

2013 Ft. Lauderdale, FL Faculty (CME Course): Winter Oncology Symposium – Holy Cross Hospital
2013  Waltham, MA  Faculty (CME Course): Men’s Health Symposium – Prostate Cancer: Screening, Management and Controversy
2013  Chicago, IL  Faculty (CME Course): Radiologic Society of North America – Refresher course: Small renal mass (T1a) – the case for resection
2014  Cambridge, MA  Faculty (CME Course): Primary Care Internal Medicine: Principles & Practice – Male Urology [Invited Lecture]
2014  Boston, MA  Faculty (CME Course): 17th Biennial Urologic Cancer Course – Bladder Cancer Biomarkers
2014  Chicago, IL  Faculty (CME Course): Radiologic Society of North America – Refresher course: Small renal mass (T1a) – the case for resection
2015  Video Series  Faculty (CME Course): Comprehensive Review of Urology – Penile and Urethral Cancer

Report of Regional, National and International Invited Teaching and Presentations

Local Invited Presentations and Courses
2008  Boston, MA  Comparative Analysis of Nephron Sparing Techniques. Update on Urologic Oncology – Massachusetts General Hospital, Harvard Medical School [Invited Lecture]
2008  Boston, MA  Prostate Cancer: Diagnosis and Management. Prostate Cancer Support Group, Massachusetts General Hospital [Invited Lecture]
2011  Boston, MA  Controversies Around the Management of Small Renal Masses – DF/HCC Kidney Cancer Program [Invited Lecture]
2011  Boston, MA  Proteomic Discovery of Novel Biomarkers in Prostate Cancer – Massachusetts General Hospital Department of Urology Centennial Academic Program [Invited Lecture]
2011  Cambridge, MA  Management of Small Renal Masses – Harvard University Health Services Grand Rounds [Invited Lecture]
2011  Boston, MA  Incidental Radiologic Findings: "Incidental Renal Masses" – Massachusetts General Hospital Medical Grand Rounds [Invited Lecture]
2012  Concord, MA  Controversies in the Management of the Small Renal Mass – Emerson Hospital Medical Grand Rounds [Invited Lecture]
2014  Boston, MA  Management of Renal Lesions in Tuberous Sclerosis Complex – Massachusetts General Hospital Department of Pathology Grand Rounds [Invited Lecture]

Regional Invited Presentations and Courses
2009  Dedham, MA  Urologic Oncology: An Overview. Massachusetts Health Information Management Association [Invited Lecture]
2010  Mt. Kisco, NY  Controversies in the Management of Small Renal Masses [Invited Lecture]
2011  Dedham, MA  Penile Cancer. Urology Nursing Society [Invited Lecture]
2012  Boston, MA  AUA Update in Bladder and Prostate Cancer. AUA New England Section, Annual Meeting
<table>
<thead>
<tr>
<th>Year</th>
<th>Location</th>
<th>Event Description</th>
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<tbody>
<tr>
<td>2013</td>
<td>Ft. Lauderdale, FL</td>
<td>Faculty (CME Course): Winter Ongology Symposium – Holy Cross Hospital</td>
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<tr>
<td>2013</td>
<td>Waltham, MA</td>
<td>Faculty (CME Course): Men’s Health Symposium – Prostate Cancer: Screening, Management and Controversy</td>
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<td>2009</td>
<td>Boston, MA</td>
<td>Renal Cell Carcinoma: Surgical Management at Massachusetts General Hospital. Exchange Experience Program on Renal Cancer [Invited Lecture]</td>
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<td>2009</td>
<td>Las Vegas, NV</td>
<td>Faculty (CME Course): Maximizing Bone Health for Patients With Prostate Cancer: Establishing the &quot;Who, What, Why &amp; How?&quot; [Invited Lecture]</td>
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<td>2009</td>
<td>Scottsdale, AZ</td>
<td>Faculty (CME Course): Maximizing Bone Health for Patients With Prostate Cancer: Establishing the &quot;Who, What, Why &amp; How?&quot; [Invited Lecture]</td>
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<td>2010</td>
<td>San Francisco, CA</td>
<td>Faculty (CME Course): Master Class on Integrating Novel Antiresorptive Agents into the treatment of Prostate Cancer. [Invited Lecture]</td>
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<td>2010</td>
<td>Boston, MA</td>
<td>Faculty (CME Course): Trauma and Critical Care Symposium – Penile and Genitalia Trauma. [Invited Lecture]</td>
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<td>2011</td>
<td>Boston, MA</td>
<td>Faculty (CME Course): Society of Translational Oncology Prostate Cancer Symposium – Prostate Cancer: Progress and Promise</td>
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<td>2011</td>
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<td>Faculty (CME Course): Primary Care Internal Medicine: Principles &amp; Practice – Case Studies in Urology [Invited Lecture]</td>
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<td>2013</td>
<td>New Orleans, LA</td>
<td>Faculty – 3D Laparoscopic Urology: Surgical Techniques and Hands-On</td>
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<td>2012</td>
<td>Mallorca, Spain</td>
<td>6th International Urology Forum – Renal Mass Biopsy [Invited Lecture]</td>
</tr>
</tbody>
</table>

**Report of Clinical Activities and Innovations**

**Current Licensure and Certification**

- 2002: Diplomate, National Board of Medical Examiners
- 2004: Massachusetts Registered Physician
Practice Activities
Urology/Urologic Oncology, Laparoscopy and Endourology Massachusetts General Hospital
Attending Urologic Surgeon, Polycystic Kidney Disease Clinic Massachusetts General Hospital

Report of Technological and Other Scientific Innovations

Patents
   - Potential use of biomarkers as diagnostic or prognostic markers in bladder cancer. These are currently under investigation and are not yet being used in clinical care
   - My contribution was and is the discovery and analysis of the patented biomarkers

Report of Education of Patients and Service to the Community

Activities

Education Material for Patients and the Lay Community:

Report of Scholarship

Peer Reviewed Publications in print or other media:

Research Investigations:


*Co-first Authorship

Other peer-reviewed publications:


Non-peer reviewed scientific or medical publications/materials in print or other media:


**Thesis**


**Abstracts, Poster Presentations and Exhibits Presented at Professional Meetings:**


23. Siddiqui MM, Heney N, McDougal WS, **Feldman AS**. Private vs. public insurance: is there a


