University of Kentucky
Department of Urology

Our Past
- Brief look at our history
- Accomplishments of our graduates

Our Present
- Growth to a Department of Urology
- Diverse faculty specialties
- Research

Our Future
Urology, also known as genitourinary surgery, is the branch of medicine that focuses on the surgical and medical diseases of the male and female urinary tract systems and the male reproductive organs.
The Division of Urology was established in 1960 with the opening of the Medical School.

- **1960**: Dr. Edward H. Ray named Chief of the Division
- **1969 - 1972**: the Division was lead by a series of Chiefs
  - Dr. Ken Walton, Dr. John Simmons & Dr. Arthur Hellebusch
- **1972**: Dr. J. William McRoberts appointed Division Chief
- **1997**: Dr. Randall Rowland appointed Chief of Urology
- **2007**: Dr. Stephen Strup appointed Chief of Urology
- **2014**: Division of Urology reclassified to Department of Urology
  - Dr. Stephen Strup named Inaugural Chair
UK Urology: Our Graduates

- 94 Graduates
- Approximately
  - 60% practice
  - 40% fellowship
- 4 Department Chairmen
- 2 Division Chiefs

Chandler Hospital
2nd Floor
Medical South “Hall of Fame”
UK Urology

Faculty

Residents

Research

Clinical Staff
UK Urology: Growth

[1] Work Relative Value Units: method of calculating the volume of work or effort expended by a physician in treating patients.
UK Urology: Clinic Growth

All Patient Visits

2010 2011 2012 2013 2014 2015

0 5,000 10,000 15,000 20,000 25,000
UK Urology: Subspecialty Organization

- Urologic Oncology/MIS Oncology
  *Multidisciplinary Cancer Care through Markey Cancer Center*
  - Stephen Strup, MD
  - Andrew James, MD
  - Cinnamon Morris, NP

- MIS/Endourology

- Complex stone disease/Robotic surgery
  - Jason Bylund, MD
  - Recruiting for Dr. Venkatesh replacement

- Female Urology/Pelvic Reconstruction
  - Deborah Erickson, MD
  - Katie Ballert, MD
  - Amber Davis, NP
  - Mary Kate Stafford, NP

- Reconstruction

- Cancer survivorship
  - Shubham Gupta, MD
  - Recruiting for second faculty

- Pediatric Urology
  - Ali Ziada, MD
  - Hannah Puntney, NP
  - Recruiting for second faculty

- General Urology
  - Jon Demos, MD
  - Matt Lawson, PA
  - David Preston, MD

- Veterans Hospital Urology
  - David Preston, MD
  - Jon Demos, MD
  - Denise Brooks, PA
Prostate Cancer Progression

Disease Burden (PSA)

Invasive Local Disease → Androgen Dependent Recurrence → Castration Resistant Prostate Cancer (CRPC)

Local Therapy:
- Brachytherapy
- External Radiation
- Radical Prostatectomy

Hormone Therapy:
- Orchietomy
- LHRH Analogues
- CYP17 Inhibitors
- Antiandrogens

Chemotherapy:
- Taxanes

Castration Resistant Prostate Cancer (CRPC)
Androgen Receptor (AR) localization and trafficking along microtubules determines therapeutic response to taxanes (Docetaxel vs Cabazitaxel)

Impact: Predicting treatment resistance to 2nd line taxane chemotherapy

EMT (Epithelial-mesenchymal transition) phenotypic profiling to predict prostate tumor progression to metastasis and therapeutic resistance

Impact: Identification/validation of biomarkers of response

Combination strategies of taxane chemotherapy and antiandrogens in androgen-responsive and castration-resistant prostate cancer (CRPC)

Impact: Overcoming mechanisms of cross-resistance by combination therapy with new Kinesin Inhibitors
Therapeutic Targeting of Microtubules: The Only Chemotherapy for Advanced Prostate Cancer

Cabazitaxel (Jevtana®)
Tubulin-Targeting Chemotherapy Impairs Androgen Receptor Activity in Prostate Cancer

Meng-Lei Zhu, Craig M. Horbinski, Mark Garzotto, et al.

Docetaxel Blocks AR Nuclear Localization in Human Prostate Cancer

Zhu et al, Cancer Res., 70:7992, 2010
PARP-1 Regulates Epithelial-Mesenchymal Transition (EMT) in Prostate Tumor Progression

Hong (1), Craig Hernderson(1,2), Patrick J. Hensley(1), Emily A. Matuszak(1), Timothy Atkinson(1) and Natasha Kyprianou(1,3,4,5)

Department of Urology and Surgery, The Markey Cancer Center, and Department of Pathology, University of Kentucky College of Medicine, Lexington, KY

BACKGROUND

Poly (ADP-ribose) polymerase (PARP) is involved in key cellular processes such as DNA replication and repair, gene transcription, cell proliferation and apoptosis (1, 2). Despite the emerging therapeutic value of PARP-1 inhibition in the treatment of advanced prostate cancer (3, 4), the role of PARP-1 in prostate cancer development and progression is not fully understood. The present study investigated the function of PARP-1 in prostate growth and tumorigenesis in vivo. Functional inactivation of PARP-1 by gene-targeted deletion led to a significant reduction in the prostate gland size in young PARP-1 +/- mice compared with wild-type (WT) littermates. To determine the effect of PARP-1 functional loss on prostate cancer onset, PARP-1 +/- mice were crossed with the transgenic TRAMP+/- model, TRAMP+/- PARP-1-/- mice exhibited higher grade prostate tumors compared with TRAMP+/- PARP-1+/+ (16-28 prostate gland size in young PARP-1-/- mice (6 weeks) compared with wild-type (WT) littermates. To determine the during prostate cancer progression is of translational significance for optimizing PARP-1 therapeutic targeting and PARP-1 function promotes prostate tumorigenesis in vivo via TGF-β signaling. 

METHODS

1. Transgenic Mouse Models: TRAMP+/+ (FVB strain) and TRAMP-/- (C57BL/6J strain) were from Jackson Laboratories.

2. Immunohistochemical Analysis: Tissue specimens were fixed in 10% buffered formalin and processed for paraffin-embedded tissue sections with the DAKO Autostainer (DAKO Cytomation, Carpinteria, CA). Representative samples were examined and, when needed, additional sections were stained for specific biotinylated antibodies as described below.

3. Apoptosis Detection: The incidence of apoptosis was evaluated in situ with a terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end labeling (TUNEL) assay.

4. Western Blot Analysis: Protein tissue was homogenized in Triton X-100 RIPA Buffer and separated by SDS-PAGE and transferred to nitrocellulose membrane. Membranes were blocked with 5% non-fat milk in TBS-T and incubated with primary antibodies overnight at 4°C. Membranes were washed three times for 15 min in TBS-T and then incubated with donkey anti-rabbit, anti-mouse, or anti-goat secondary antibodies conjugated with horseradish peroxidase. Membranes were washed and visualized using an enhanced chemiluminescence (ECL) detection system (Amersham). Protein bands were quantified using an image analysis system.

RESULTS

Figure 1: TUNEL staining of prostate tissue from PARP-1+/+ and PARP-1-/- of mice. B. shows the weights of the prostate glands. C. reveals the TUNEL staining of prostate tumor samples. Figure 2: Western blot analysis of cell lysates from prostate tissue of mice. E, values indicate the average number TUNEL-positive cells per field. Figure 3: Western blot analysis of cell lysates from prostate tissue of mice. E, values indicate the average number TUNEL-positive cells per field. Figure 4: Relative E-cadherin mRNA expression in prostate tissue from three different groups of TRAMP+/-, PARP-1+/+ and PARP-1-/- mice. Panel A reveals intense nuclear AR immunoreactivity for the TGF-β signaling effectors. Panel B shows comparative protein profiling by Western Blot analysis of prostate tissue lysates, indicating potential novel targets for future investigation.
Reversion of EMT to Mesenchymal to Epithelial Transition (MET) in CRPC by Cabazitaxel Chemotherapy

E-Cadherin

VHC

MDV

CBZ

MDV+CBZ

Epithelial phenotype

Intermediate phenotypes as cells transition

Mesenchymal phenotype

Epithelial cells

E-cadherin
Cytokeratin
ZO-1
Laminin-1
Entactin

Syndecan
MUC1
Desmoplakin
α1 (IV) collagen
miR200 family

Progressive loss of epithelial markers and gain of mesenchymal markers

FTS binding protein FAP
FSP-1
N-cadherin
Vimentin
Fibronectin
β-catenin
Ob-cadherin
α5β1 integrin
Syndecan-1
miR10b
Snail
Slug
ETS
SIP1
α-SMA
Twist
Goosecoid
LEF-1
FOXC2
miR21
During EMT, loss of cell polarity and mesenchymal phenotype promote invasion and resistance.
Collaboration with Dr. Marianne Sadar
Development of Novel Antiandrogen (EPI): In Phase I Clinical Trials

Regression of Castrate-Recurrent Prostate Cancer by a Small-Molecule Inhibitor of the Amino-Terminus Domain of the Androgen Receptor

Raymond J. Andersen, Nasrin R. Mawji, Jun Wang, Gang Wang, Simon Halle, Jae-Kyung Myung, Kate Watt, Teresa Tam, Yu Chi Yang, Carmen A. Baruelos, David E. Williams, Iain J. McEwan, Yuzhou Wang, and Marianne D. Sadar.
Translational Significance

Predicting resistance in patients:

- Impact of AR (Androgen Receptor) variants in therapeutic resistance to combination therapy
- AR-V7 predict response to enzalutamide in prostate cancer

Antonarakis et al, NEJM 2014
Additional Research Activity

Dr. Hong Pu

1. Development and characterization of Mouse Models of EMT-driven progression in advanced prostate cancer
2. Training of medical students and urology residents in translational research, genetic analysis, biomarker detection
3. Therapeutic targeting / treatment optimization in Vivo
4. Clinical research in urologic oncology, stone disease, reconstruction, female pelvic surgery, pediatric urology
<table>
<thead>
<tr>
<th>Protocol</th>
<th>Title</th>
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<tbody>
<tr>
<td>15-GU-67-HR</td>
<td>Patients with PD-L1 selected, high risk muscle invasive bladder cancer after cystectomy</td>
</tr>
<tr>
<td>14-GU-65-TP</td>
<td>Patients with advanced or metastatic renal cell carcinoma</td>
</tr>
<tr>
<td>NCI-CIRB-S1216</td>
<td>Patients with newly diagnosed metastatic hormone sensitive prostate cancer</td>
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<tr>
<td>13-RAD-01</td>
<td>Megavoltage imaging to reduce artifact following interstitial seed implants for prostate adenocarcinoma</td>
</tr>
<tr>
<td>2010-052</td>
<td>Tracking renal tumors after cryoablation evaluation (TRACE)</td>
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UK Urology: Residents

Faculty

Residents

Research

Clinical Staff
Desirable Residency Program

- Reputation as strong teaching program/faculty
- Balanced program with all strong subspecialty representation

In a very competitive match environment, we have matched residents from the top of our match list each year

- Strong UK student interest in Urology
- Adding a third resident per year beginning in 2016
UK Urology: Clinical Staff
UK Urology: Clinic Staff

- Practice Manager
  - Tina Petot

- Clinical Services Technicians
  - Brittney Chism
  - Doneka Farris-Young
  - Teresa Warren
  - April Washington

- Licensed Practical Nurse
  - Rebecca Meade

- Patient Services Coordinator
  - Megan Reese
  - Leah Ritchey

- Patient Relations Associate
  - Debbie Isenhoff

- Patient Relations Assistant
  - Amanda Sallee
  - Rob Wardlow-Todd

- Medical Records Clerk
  - Christy Hadley

- Staff Support Associate
  - Ronda Hunt

- Administrative Services Assistant
  - Patricia Foster

- Staff Support Associate
  - Lorie Howard
  - Sheila Sexton

- Growth
  - Clinical Services Technician
  - Registered Nurse
UK Urology: New Clinical Office (May 2016)
UK Urology: 2016

- Rich history which has grown with UK HealthCare
- Talented, diverse group of faculty that cover the spectrum of urologic care
- Solid, desirable residency program
- Productive research core
- Practicing “quality” patient care as we are consistently “green across the board” with length of stay, mortality, physician communication and 30-day readmission rates
UK Urology: The Future

Challenge: Growth and change to meet the evolving health care delivery system
Contemplate adding general urology core group of faculty to meet the needs of the UK HealthCare collaborative effort.

Continue to grow our basic science and clinical research efforts with emphasis on prostate and bladder cancer.

Expand our clinical trial portfolio to support the Markey Cancer Center and deliver cutting edge cancer care.

Continue to emphasize our resident education program as medical education changes with healthcare reform.
UK Urology

Thank you!