Urology
Past, Present & Future

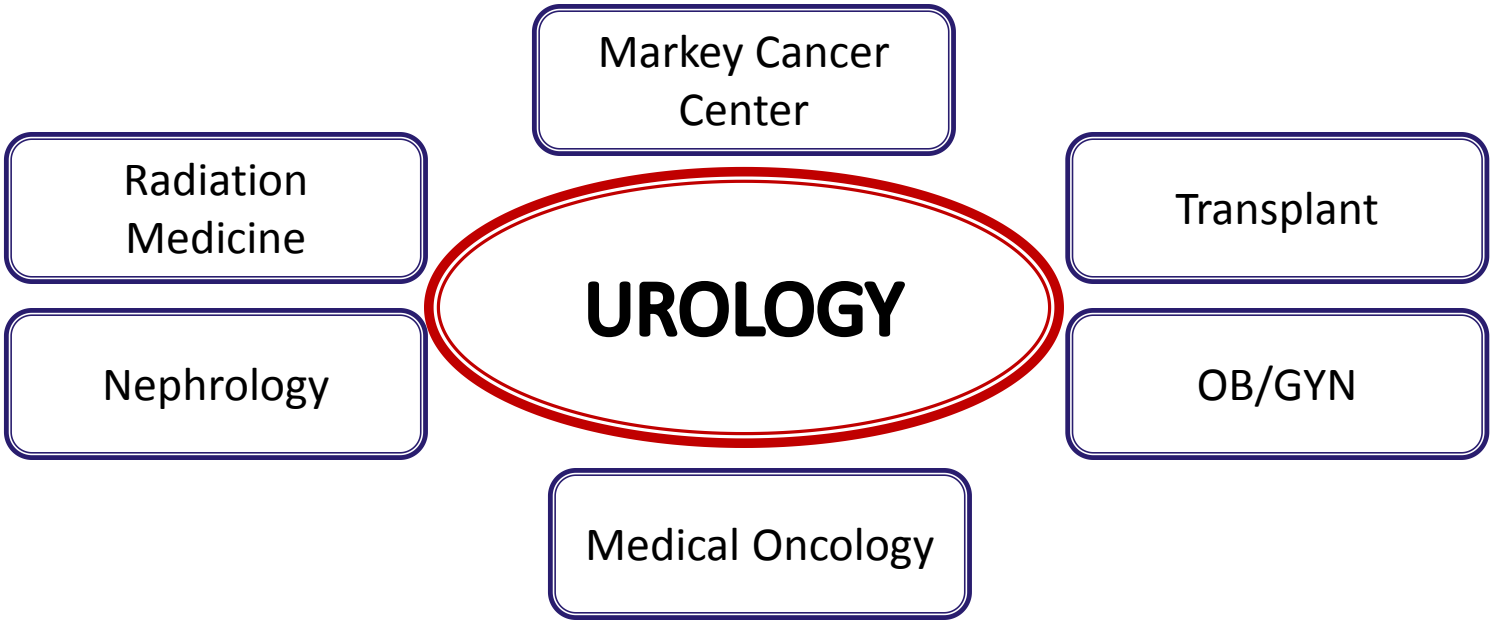
Stephen E. Strup, MD, FACS
James F. Glenn Professor and Chair
Department of Urology

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

What is Urology?

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



UK Urology: Historical Notes

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 HealthCare

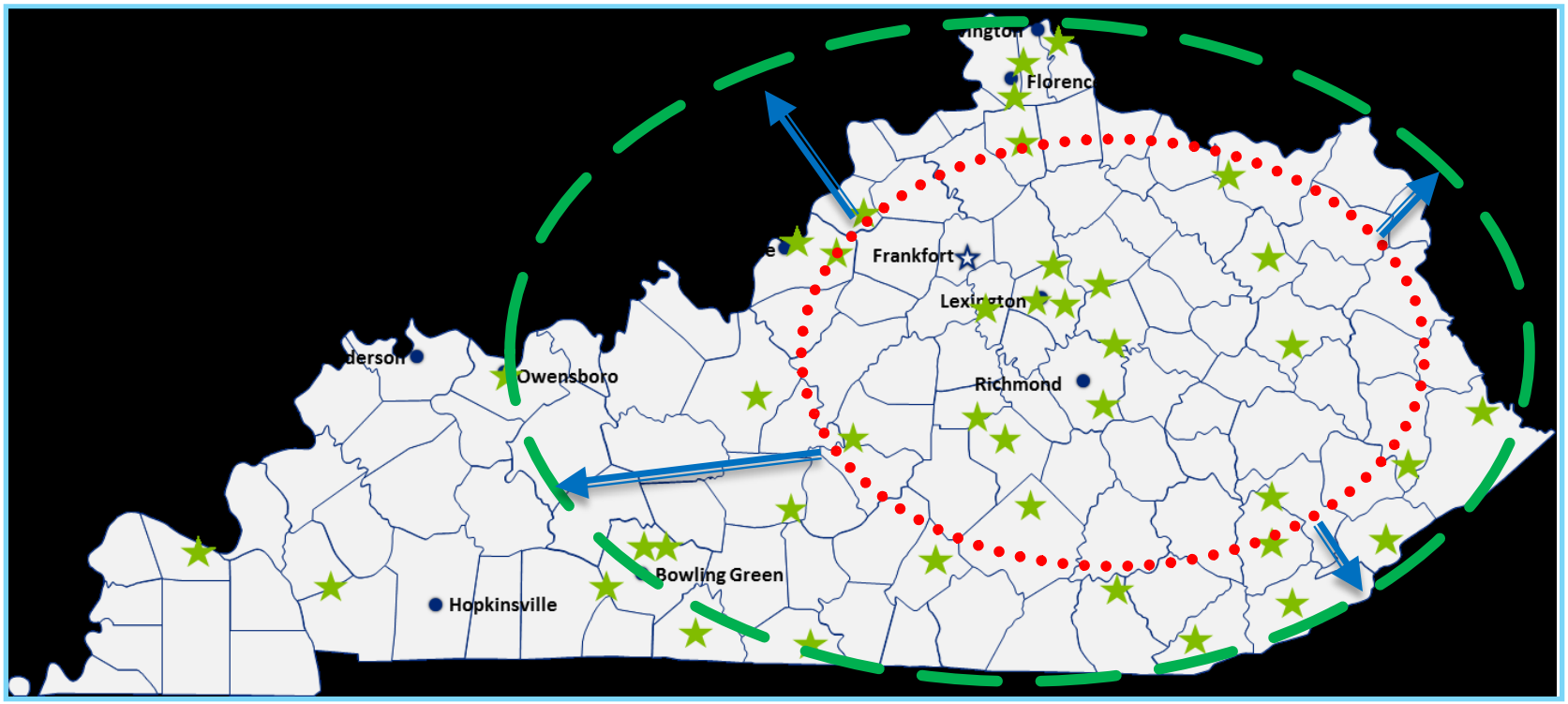
UK Urology: Present

UK HealthCare

UK Urology

HealthCare

UK Urology: Growth



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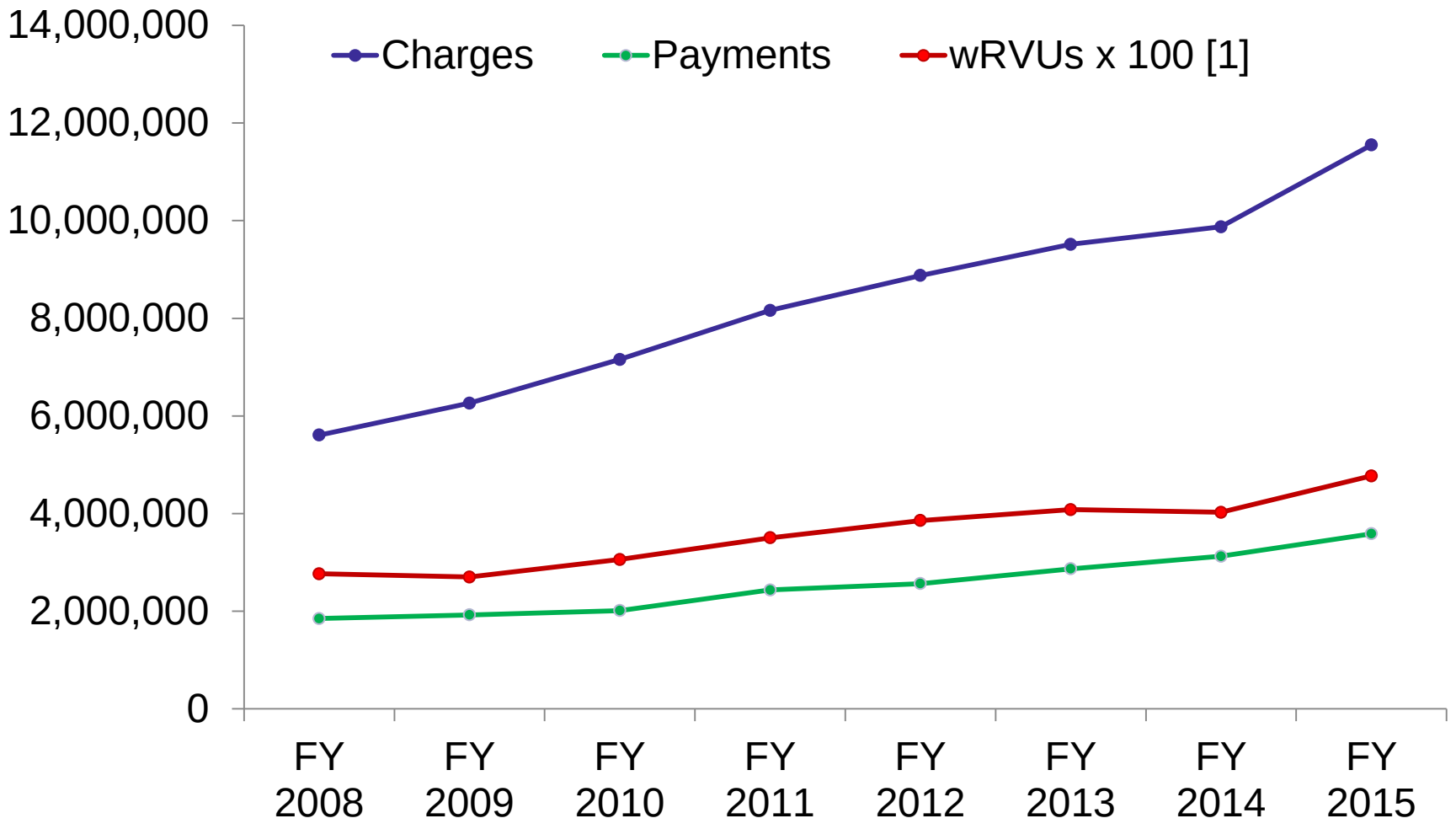
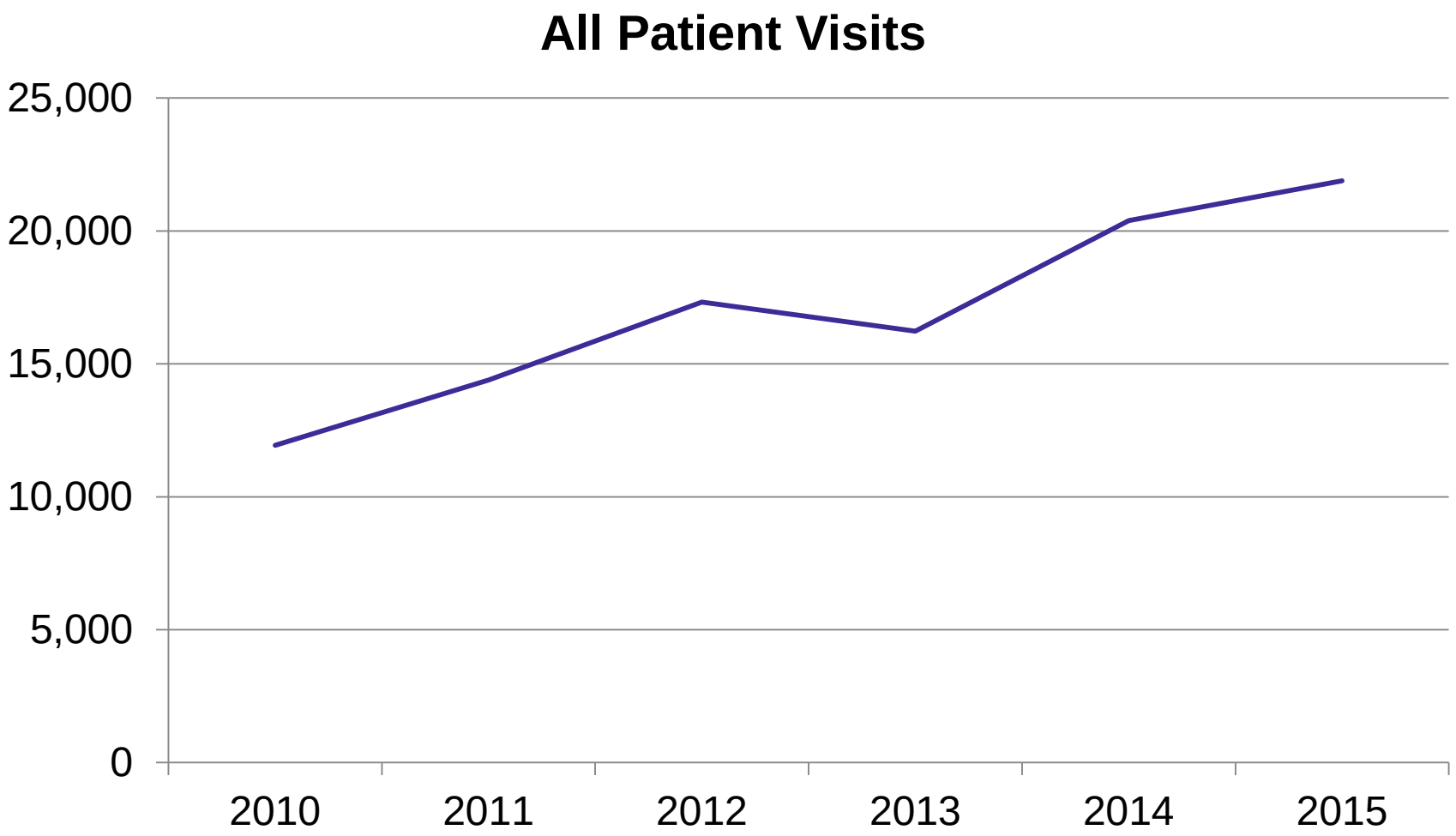
UK Urology: Growth



[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



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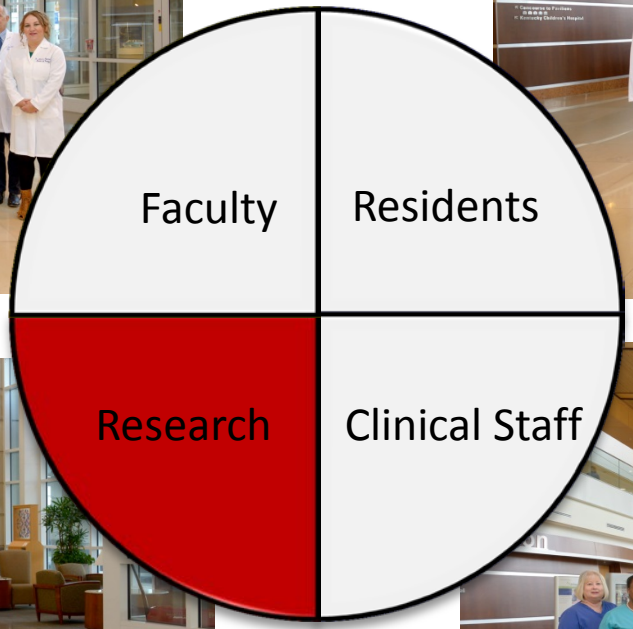
UK Urology: Subspecialty Organization

- 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

UK Urology: Research



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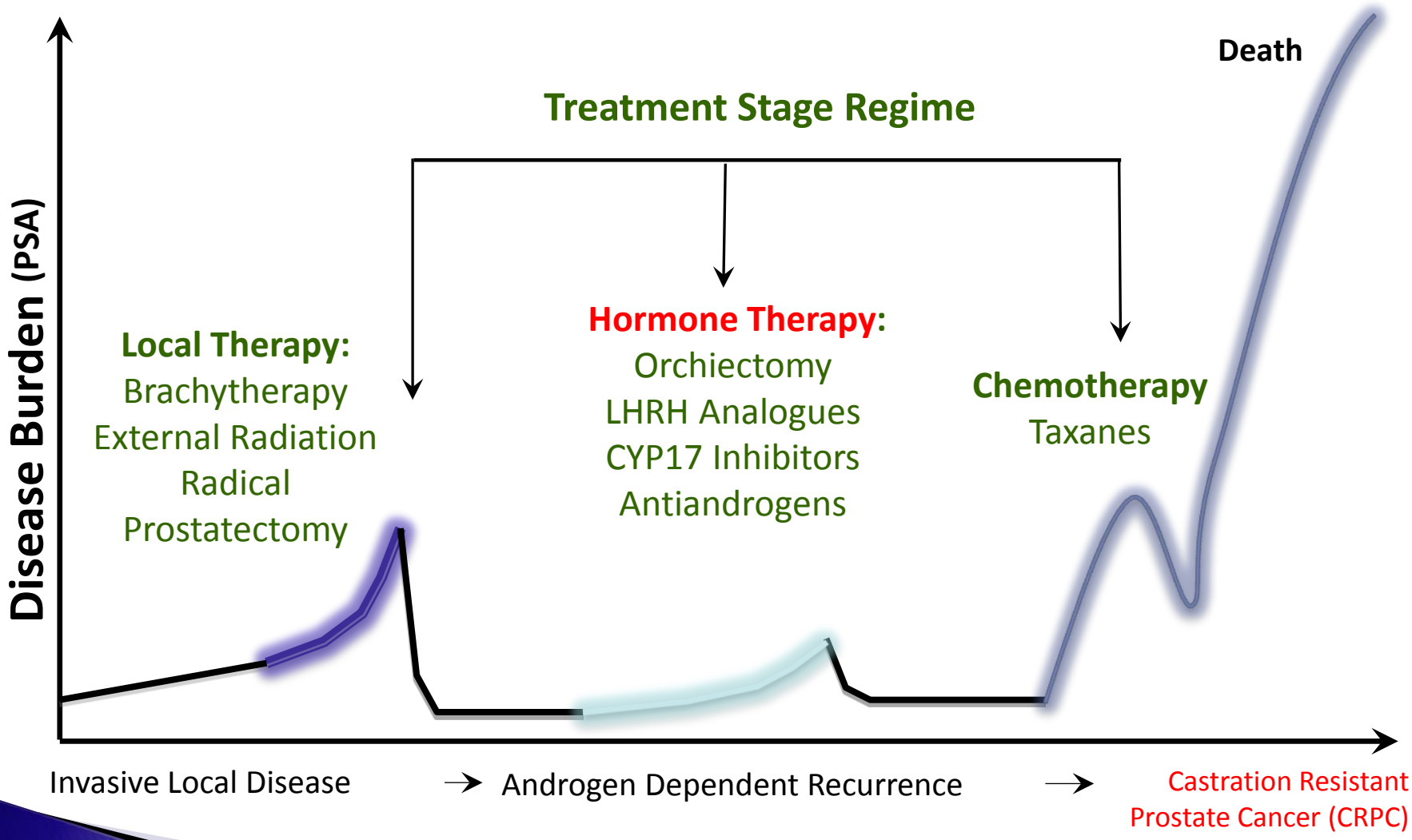
Prostate Cancer Progression



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Significance of UK-Urology Research
Prostate Cancer Focus

- **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

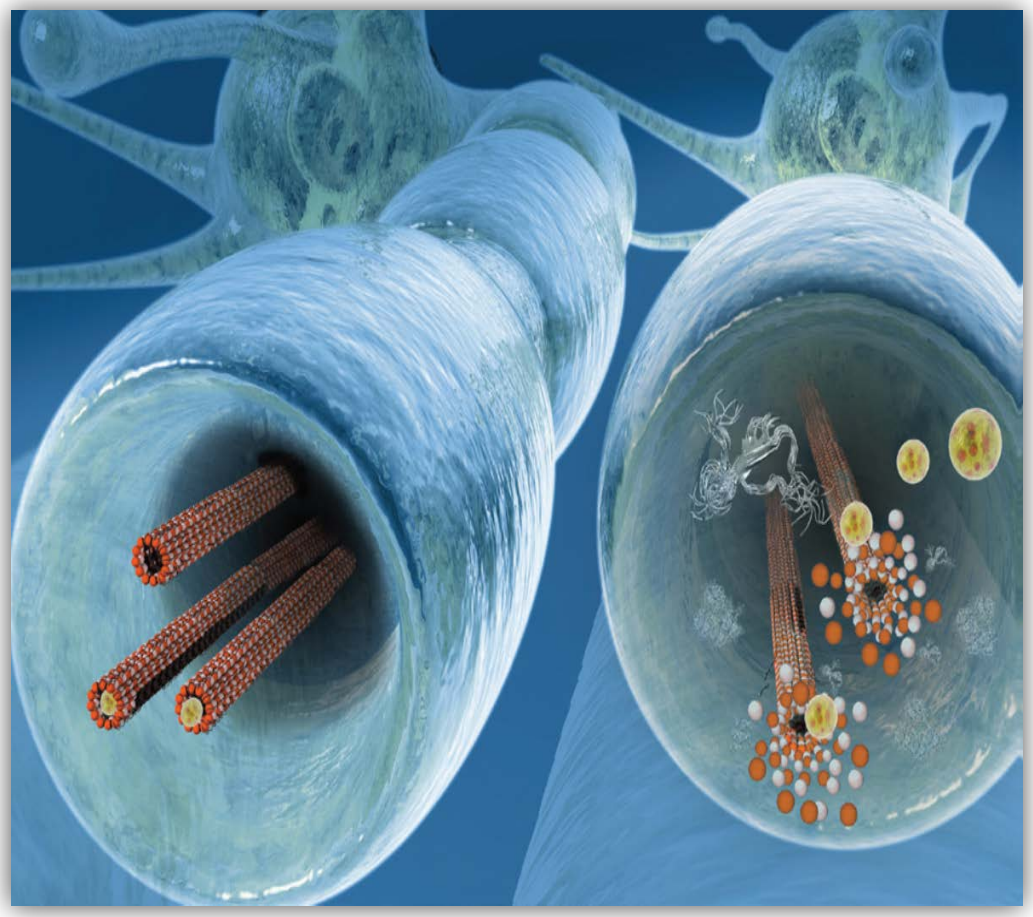
- **EMT (Epithelial-mesenchymal transition) phenotypic profiling to predict prostate tumor progression to metastasis and therapeutic resistance**

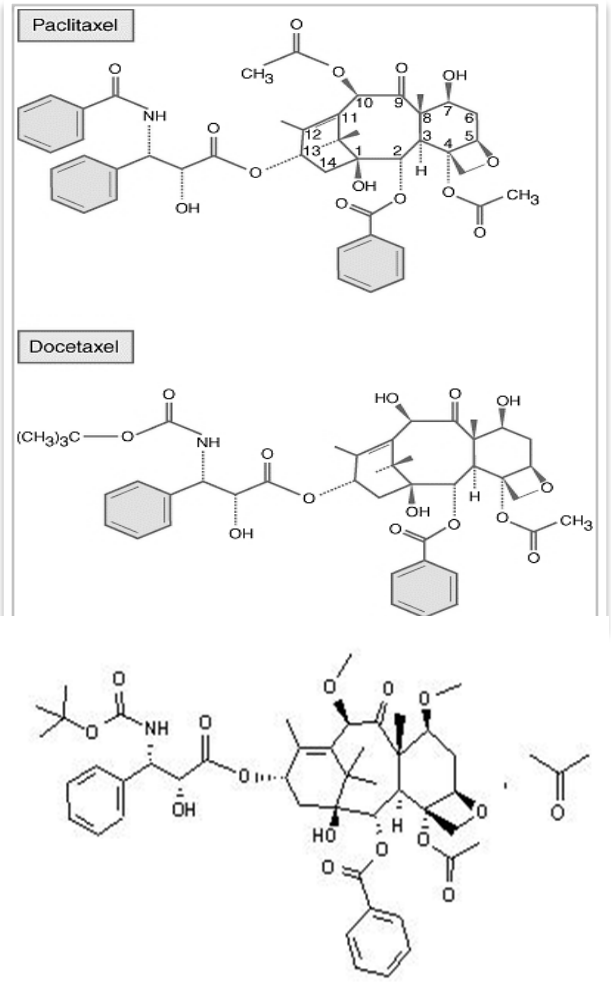
  Impact: Identification/validation of biomarkers of response

- **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©)

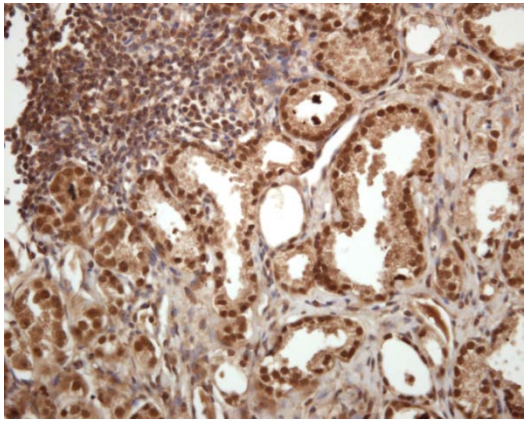
UK HealthCare

Tubulin-Targeting Chemotherapy Impairs Androgen Receptor Activity in Prostate Cancer

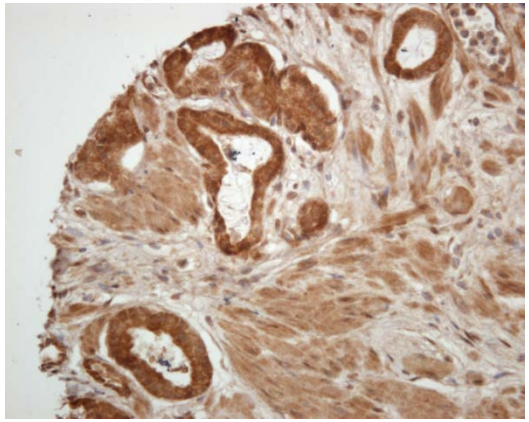
Meng-Lei Zhu, Craig M. Horbinski, Mark Garzotto, et al.

Docetaxel Blocks AR Nuclear Localization in Human Prostate Cancer

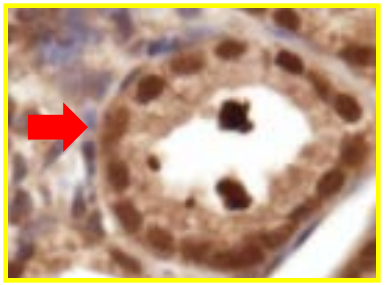
Meng Lei Zhu, MD, PhD

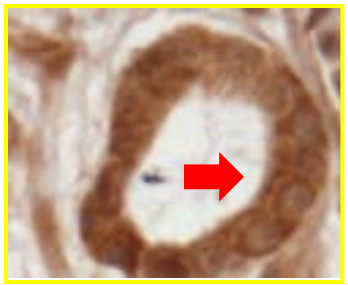


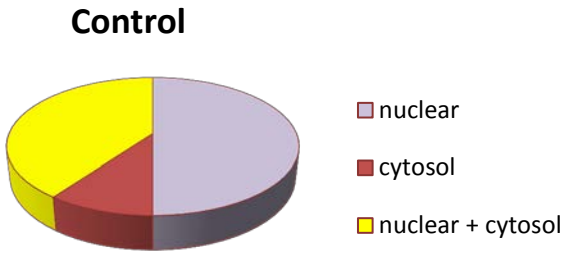
Control

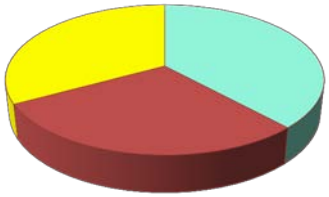


Docetaxel









Zhu et al, Cancer Res., 70:7992, 2010

HealthCare

PARP-1 Regulates Epithelial-Mesenchymal Transition (EMT) in Prostate Tumor Progression

Hong Pu[1], Craig Horbinski[2,3,4] Patrick J. Hensley[1], Emily A. Matuszak[5], Timothy Atkinson[1], and Natasha Kyprianou[1,2,3,4,5]
Departments of Urology[1] and Pathology[2] and Biochemistry[3], the Markey Cancer Center[4], and Department of Toxicology[5] , 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 inhibitors 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 (6 weeks) 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 adenocarcinoma of the mouse prostate (TRAMP) mice. Pathological assessment of prostate tumors revealed that TRAMP+/-, PARP-1-/- mice exhibited higher grade prostate tumors compared with TRAMP+/- PARP-1+/+ (16-28 weeks) that was associated with a significantly increased proliferative index and decreased apoptosis among the epithelial cells in TRAMP+/- PARP-1-/- prostate tumors. Furthermore tumors harboring PARP-1 loss, exhibited a downregulation of nuclear androgen receptor. Impairing PARP-1 led to increased levels of transforming growth factor-β (TGF-β) and Smads that correlated with induction of epithelial-mesenchymal transition (EMT), as established by loss of E-cadherin and β-catenin and upregulation of N-cadherin and ZEB-1. Our findings suggest that impaired PARP-1 function promotes prostate tumorigenesis in vivo via TGF-β-induced EMT. Defining the EMT control by PARP-1 during prostate cancer progression is of translational significance for optimizing PARP-1 therapeutic targeting and predicting response in metastatic castration-resistant prostate cancer (5, 6).

METHODS

- **1. Transgenic Mouse Models:** TRAMP-/-,PARP-1+/- males were crossed to TRAMP+/-,PARP-1+/- females in C57BL/6 background. TRAMP and PARP-1 mice are from Jackson Laboratories.
- **2. Immunohistochemical Analysis:** Tissue specimens are fixed in 10% (v/v) formalin and formalin-fixed paraffin-embedded tissue specimens were deparaffinized, rehydrated, and subjected to H&E and immunostaining using specific antibodies.
- **3. Apoptosis Detection:** The incidence of apoptosis was evaluated *in situ* using the terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end labeling (TUNEL) assay.
- **4. Western Blot Analysis:** Prostate tissue was homogenized in TRIzol Reagent and NE-PER Nuclear and Cytoplasmic Extraction Reagents (Pierce Biotechnology, Rockford, IL). Whole tissue protein, cytoplasmic and nuclear protein were extracted following the manufacturer's instructions.
- **5. Real-time PCR Analysis:** Total RNA was extracted from prostate tissue using the TRIzol Reagent and 1μg was reverse transcribed into cDNA using a reverse transcription kit from Promega. Real-time PCR was conducted is an ABI Prism 7300 system (Applied Biosystems).

RESULTS

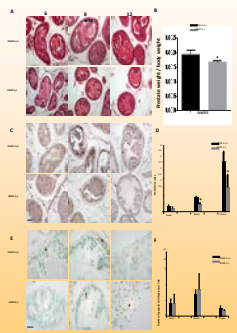


Figure 1. Reduction in prostate glands in PARP-1-/- mice due to decreased proliferative activity. A. reveals H&E staining of prostate tissue from PARP-1+/+ and PARP-1-/- of mice. B. shows the weights of the prostate glands. C. indicates the KI-67 nuclear antigen immunoreactivity. D. represents the quantitative analysis of the data from C. E. reveals TUNEL staining for apoptosis detection in prostate tissue from PARP-1+/+ and PARP-/- mice. F, indicates the quantitative analysis of TUNEL positive cells. (Mice are 6, 8 and 12 -wks).

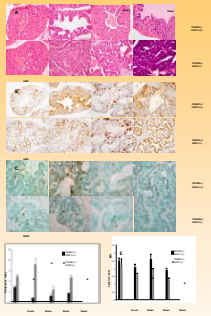


Figure 2. PARP-1 functional loss in TRAMP model increases prostate tumor aggressiveness via induced cell proliferation and apoptosis reduction. A, Histological evaluation of prostate tissue from TRAMP+/- PARP-1+/+ and TRAMP+/-PARP-1-/- mice by H&E staining. B, the prostate cell proliferative index in tumors from TRAMP+/- PARP-1+/+ and TRAMP+/- PARP-1-/- mice. Quantitative analysis of Ki-67 staining is shown on Panel D; C reveals the TUNEL staining of prostate tumor apoptotic cells from TRAMP+/- PARP-1+/+ and TRAMP+/- PARP-1-/- mice. E, values indicate the average number TUNEL-positive cells per higher field +/-SEM (three fields). Mice are 16, 20, 24 and 28-wks.

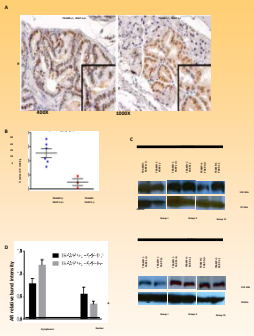


Figure 3. Loss of PARP-1 reduces AR nuclear localization and activity. A, AR localization and immunoreactivity in prostate tissues from TRAMP+/- PARP+/+ and TRAMP+/- PARP-1-/- mice (20-wks). B, Quantitative analysis of data from A. C, Western blot analysis of cytoplasmic and nuclear fractions from prostate tissue lysates. D, densitometry from C.

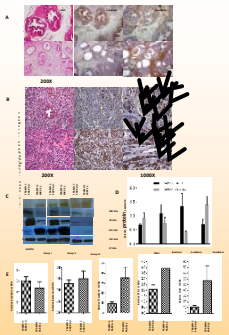


Figure 4. PARP-1 deficiency yields acquisition of EMT phenotype during prostate tumorigenesis. Panel A, E-cadherin and N-cadherin in prostate tissue from TRAMP+/- PARP-1+/+ and TRAMP+/- PARP-1-/- mice (28-wks). Panel B, reveals immunoreactivity pattern for ZEB1 in prostate tumor sections from TRAMP+/-/PARP-1 +/+ and TRAMP+/-/PARP-1 -/- mice. H&E (left), Panel C shows Western blot analysis of EMT regulators ZEB-1, E-cadherin, N-cadherin, β-catenin expression in prostate tissue from three different groups of TRAMP+/- PARP-1+/+and TRAMP+/- PARP-1-/- mice (16-wks). Panel D, the barographs indicate the relative band intensity (from Panel C). Panel E shows mRNA profile by RT-PCR analysis of E-cadherin, β-*catenin, N-cadherin, ZEB-1* and *Twist* gene expression in TRAMP+/- PARP-1+/+ vs. TRAMP+/- PARP-1-/-mice (16-wks).

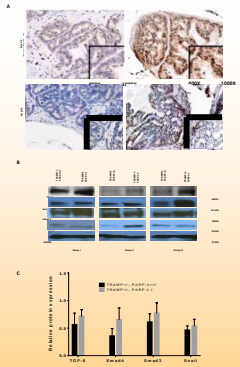


Figure 5. Dysfunctional PARP-1 Induces TGF-β mediated EMT in prostate tumors. Analysis of expression of TGF-β signaling effectors. Panel A reveals intense nuclear immunoreactivity for the TGF-β intracellular effector, Smad3 protein in prostate tumor cells in tissue specimens from TRAMP+/- PARP-1-/- mice, compared to age-matched TRAMP+/- PARP-1+/+ mice. Panel B, comparative protein profiling by Western blot analysis of prostate tumor lysates for TGF-β (ligand) and its main intracellular effectors Smad 3 and Smad4 in TRAMP+/- PARP-1 -/- prostate tumors vs *WT* mice. Panel C, indicates the results of densitometric analysis from panel B.

CONCLUSIONS

1. **Prostate tumors harboring PARP-1 loss, exhibited a decrease in nuclear AR and an increase in TGF-β signaling that correlated with EMT induction.**
2. **Impaired PARP-1 function promotes prostate progression to metastasis *in vivo* via TGF-β induced EMT.**
3. **Novel control by PARP-1 of prostate cancer progression is of translational significance in therapeutic targeting of metastatic CRPC by PARP-1 inhibitors.**

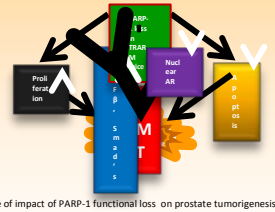


Figure 6: Significance of impact of PARP-1 functional loss on prostate tumorigenesis. PARP-1 loss induces EMT and accelerates aggressive prostate tumor growth, via a Smad-directed TGF-β signaling mechanism. A cross-signaling interaction with AR mediated by nuclear AR depletion may contribute to enhanced EMT, providing a new insight into potential mechanism of therapeutic cross-resistance between PARP-1 inhibitors and antiandrogens in the treatment of advanced prostate cancer.

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1. Gibson, BA and Kraus WL (2012) New insights into the molecular and cellular functions of poly (ADP ribose) and PARPs, Nat Rev Mol Cell Biol., 13:411-424.
2. Steffen, JD et al (2013) Targeting PARP-1 allosteric regulation offers therapeutic potential against cancer. Cancer Res. 74(1):31-37.
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6. Matuszak, E. and Kyprianou, N. (2011) Androgen regulation of epithelial-mesenchymal transition in prostate tumorigenesis. Expert Reviews in J. Clin. Endocrinol and Metabol., 6(3):469-482.

FUNDING

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CONFLICT OF INTEREST

The authors have no conflicting financial interests.

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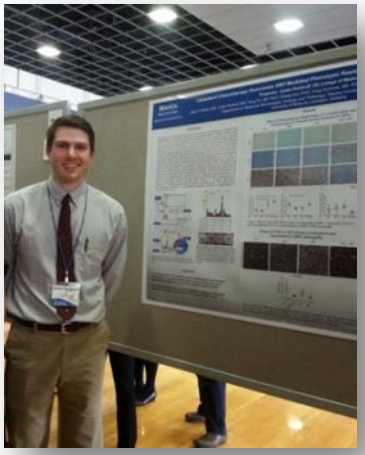
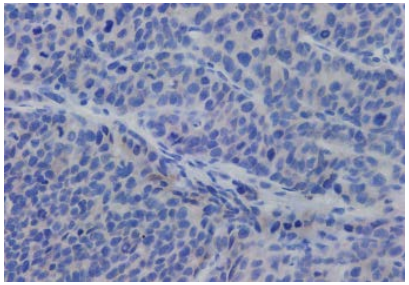
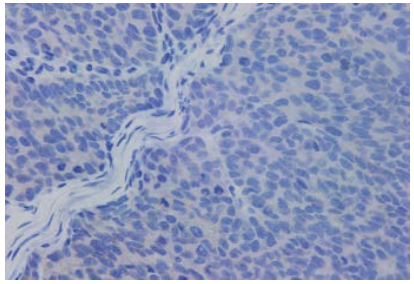
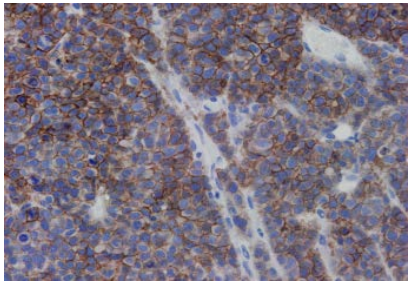
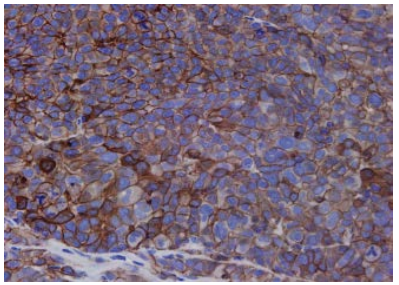
Justin Penticuff

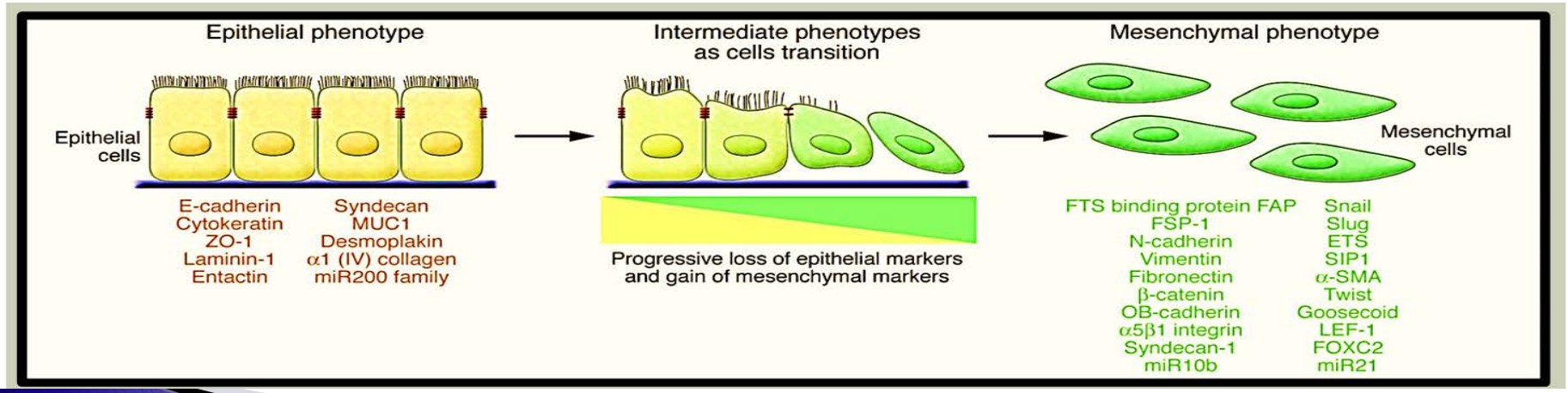


Reversion of EMT to Mesenchymal to Epithelial Transition (MET) in CRPC by Cabazitaxel Chemotherapy

VHC | MDV | CBZ | MDV+CBZ

E-Cadherin



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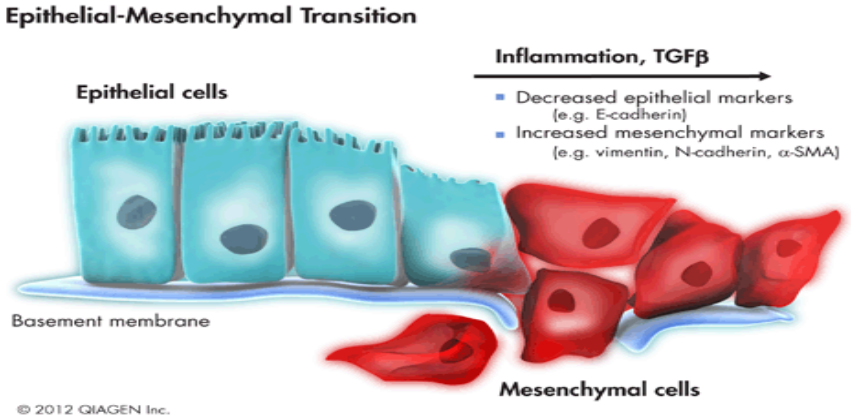
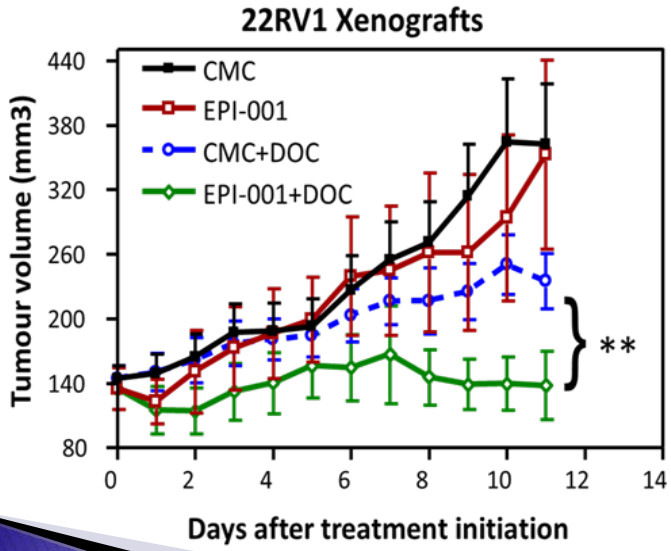
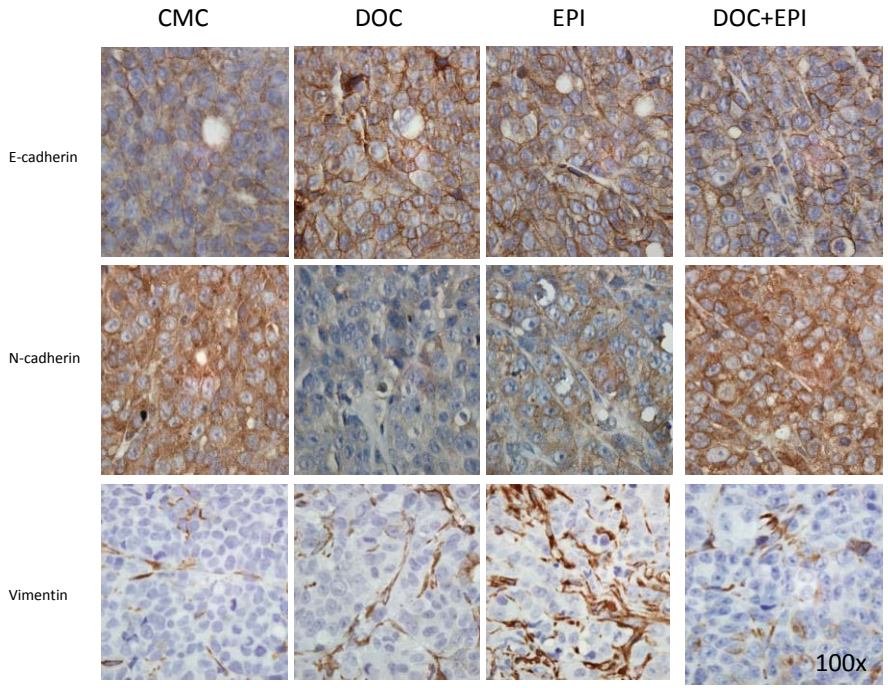
Novel Anti-androgen (EPI) Increases CRPC Response to Taxane Chemotherapy via EMT Reversion to MET



During EMT, loss of cell polarity and mesenchymal phenotype promote invasion and resistance





Martin et. al, Molecular Oncology, 2015

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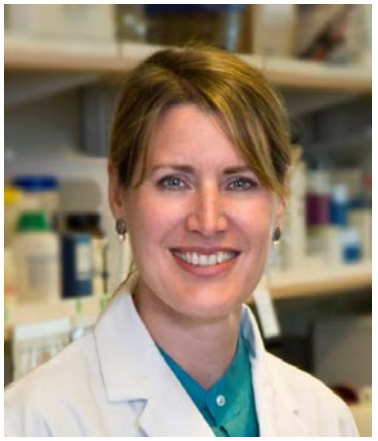
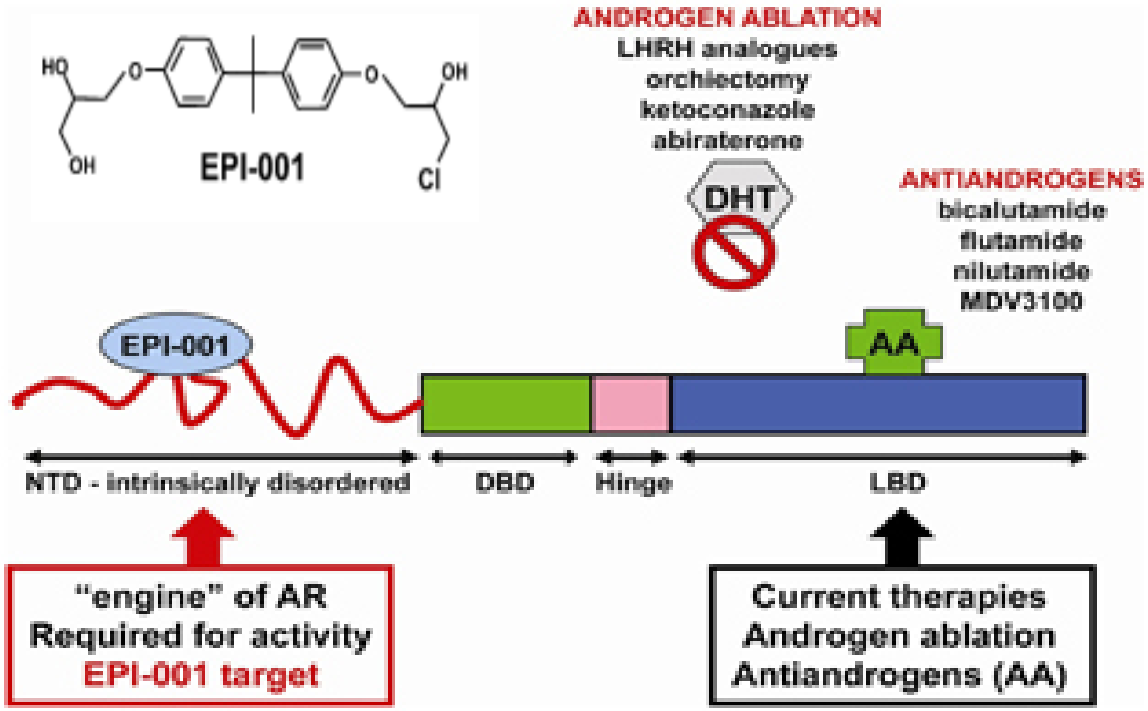
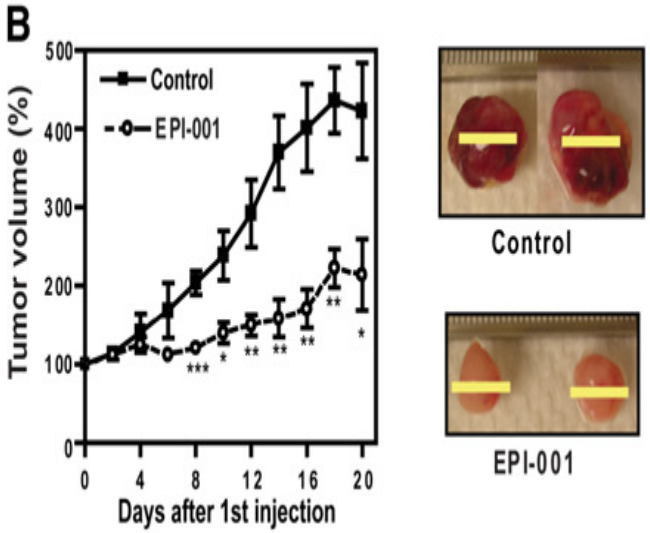
Collaboration with Dr. Marianne Sadar
Development of Novel Antiandrogen (EPI): In Phase I Clinical Trials



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

Raymond J. Andersen,[3] Nasrin R. Mawji,[1] Jun Wang,[1] Gang Wang,[1] Simon Haile,[1] Jae-Kyung Myung,[1] Kate Watt,[4] Teresa Tam,[1] Yu Chi Yang,[1] Carmen A. Bañuelos,[1] David E. Williams,[2] Iain J. McEwan,[4] Yuzhou Wang,[2] and Marianne D. Sadar[1,*]





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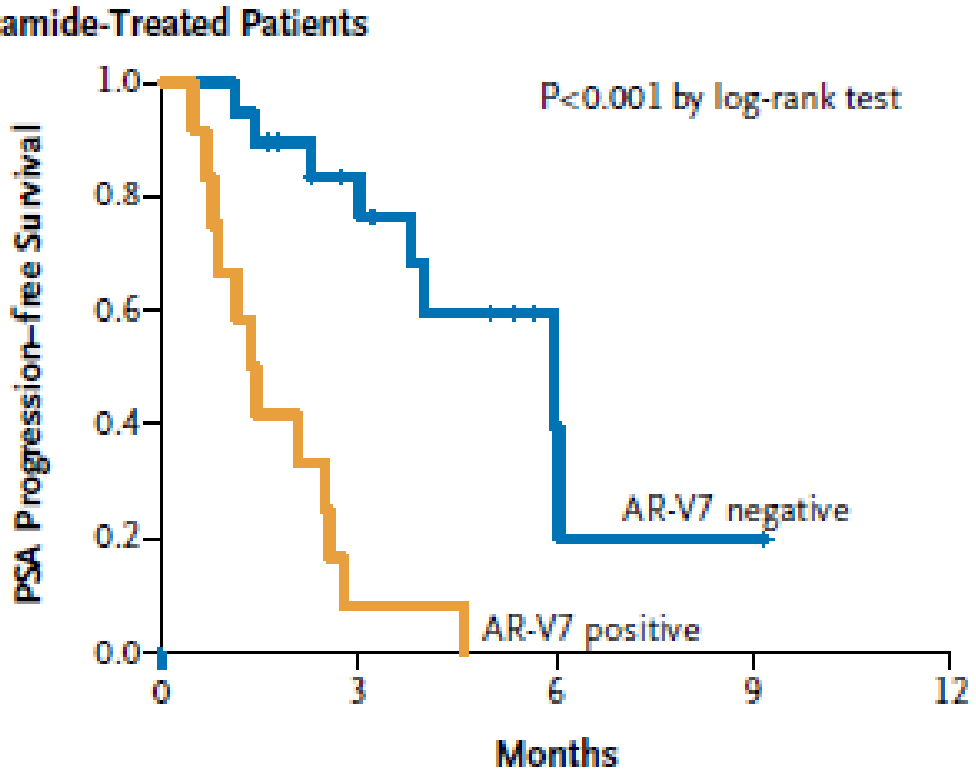
Translational Significance

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

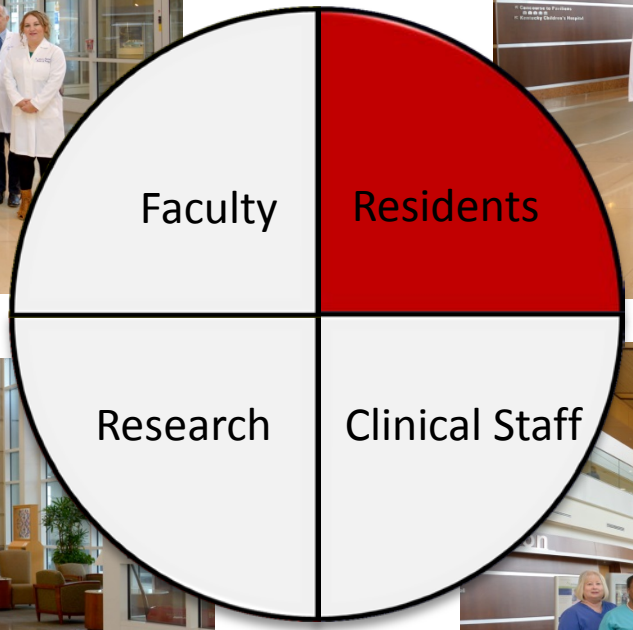
Dr. Hong Pu

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

Clinical Trials
Markey Cancer Center

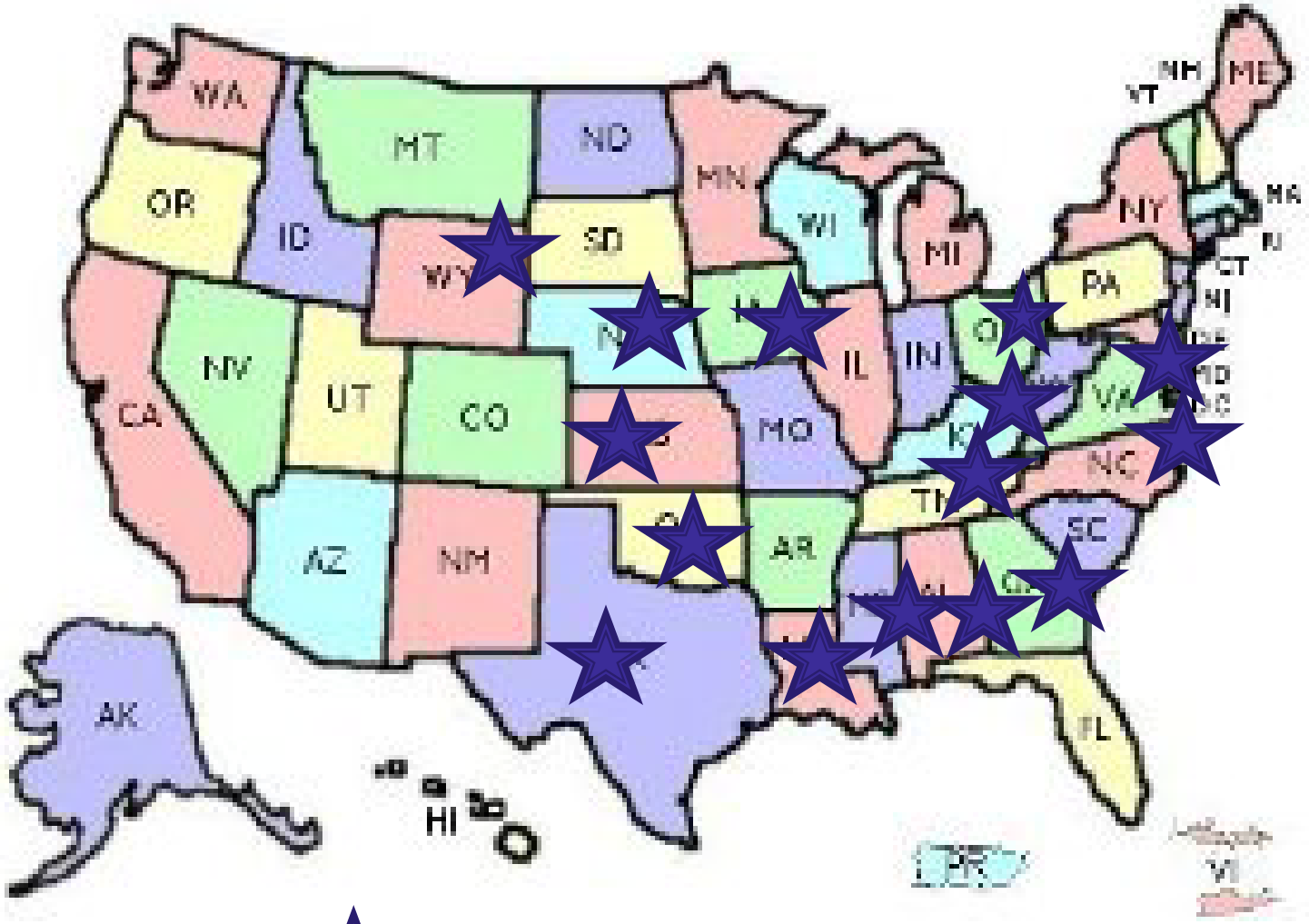
Protocol	Title
15-GU-67-HR	Patients with PD-L1 selected, high risk muscle invasive bladder cancer after cystectomy
14-GU-65-TP	Patients with advanced or metastatic renal cell carcinoma
NCI-CIRB-S1216	Patients with newly diagnosed metastatic hormone sensitive prostate cancer
13-RAD-01	Megavoltage imaging to reduce artifact following interstitial seed implants for prostate adenocarcinoma
2010-052	Tracking renal tumors after cryoablation evaluation (TRACE)

UK Urology: Residents



UK HealthCare

UK Urology: Residents



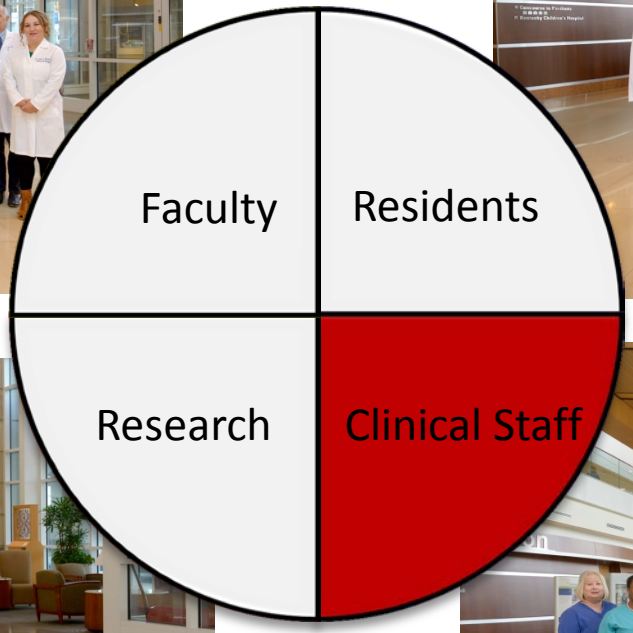
= resident from this state

HealthCare

UK Urology: Residency Program Notes

- 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



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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

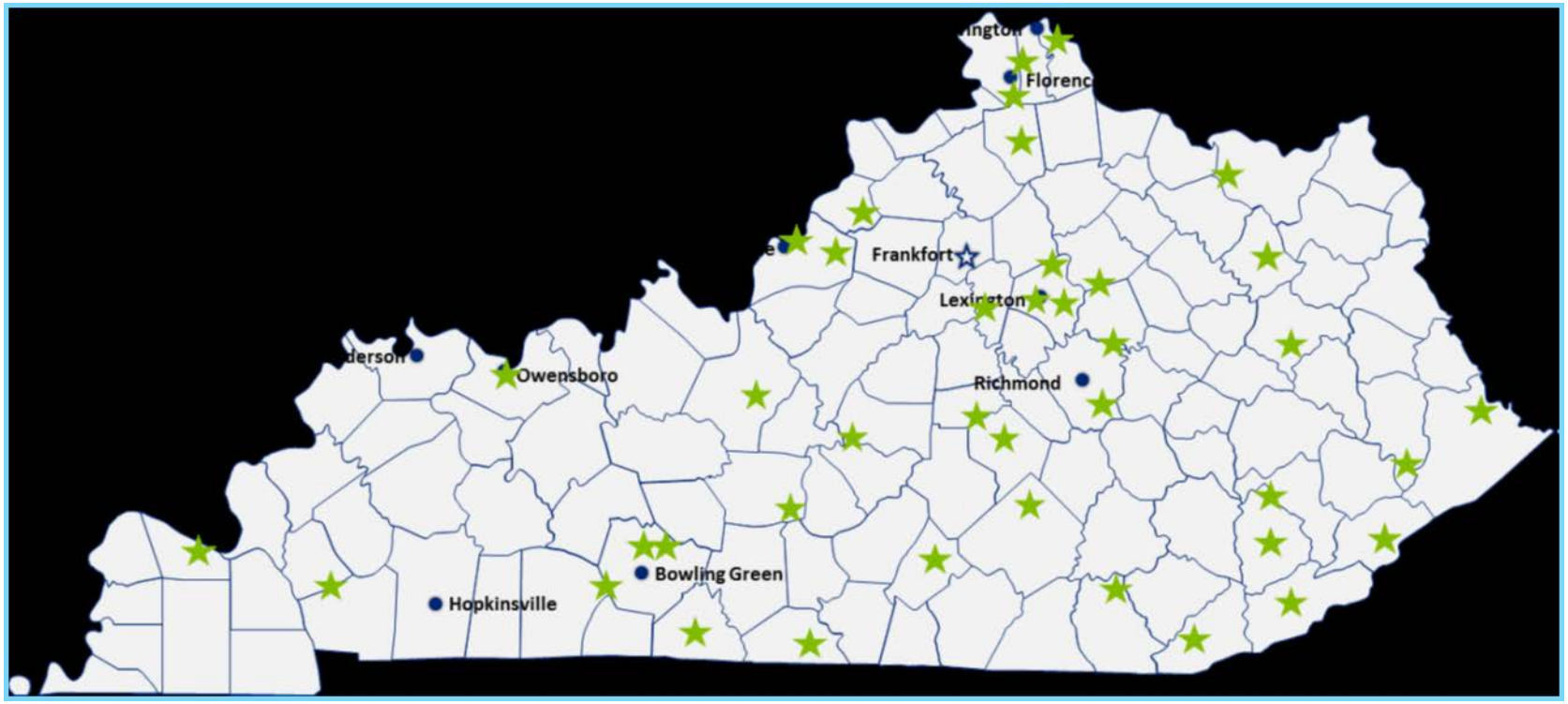
UK Urology: New Clinical Office (May 2016)

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



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UK Urology: The Future

- 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!