MESSAGE FROM THE CHAIR

Dear Colleagues,

As we begin a new year, I’m delighted to update you on the latest clinical and research news here at Wake Forest Baptist Urology. From an expanded clinical initiative for pelvic floor disorders to a project to develop a research model for post-prostatectomy incontinence and erectile dysfunction, I am proud of the innovative, pioneering spirit of our faculty.

Education is also an important part of our mission and I’m pleased to announce that we now offer four urology fellowship opportunities, including our newest offering in Female Pelvic Medicine and Reconstructive Surgery.

I hope you’ll enjoy reading about our team’s efforts to advance the field. We welcome collaborations and would be pleased to hear from you.

Anthony Atala, MD
William H. Boyce Professor and Chair

Innovations in Urology

From research on gene expression in interstitial cystitis to efforts to engineer testicular tissue in the lab, Wake Forest Baptist Health urologists are leaders in both basic science and innovative clinical therapies. Examples of current projects include:

3D Printed Tissue Closer to Reality

The idea of 3D printing replacement urologic tissues came a step closer to reality in 2016 when Wake Forest Baptist researchers reported success printing living tissue structures that developed a system of nerves and blood vessels when implanted in animals.

The potential applications for urology are varied, including printing the urologic tissues that have been engineered by hand and implanted in patients: bladder, urethra and vagina.

Reporting in *Nature Biotechnology*, the scientists said they printed ear, bone and muscle structures that have the right size, strength and function for use in humans.

With funding from the Armed Forces Institute of Regenerative Medicine, a federally funded effort to apply regenerative medicine to battlefield injuries, the team plans to implant bioprinted muscle, cartilage and bone in patients in the future.

A major challenge of tissue engineering is ensuring that implanted structures live long enough to integrate with the body. The bioprinting team addressed this by optimizing the water-based “ink” that holds the cells so that it promotes cell health and growth and by printing a lattice of microchannels throughout the structures. These channels allow nutrients and oxygen from the body to diffuse into the structures and keep them alive while they develop a system of blood vessels.
A Blood Test to Predict BCG Response? Although its mechanisms are not well understood, intravesical live Bacillus Calmette-Guérin (BCG) therapy remains the treatment of choice for bladder cancer in situ due to its response rate of up to 70 percent. But with more than 30 percent of patients failing to respond, it is possible to predict whether patients will benefit? Ronald Davis, MD, is principal investigator on a Wake Forest Baptist study evaluating whether a simple blood test can identify non-responders so they could immediately be treated with other options. The study, which involves 40 patients slated for BCG therapy, is based on research by Zheng Cui, MD, PhD, associate professor of pathology. Cui’s previous work on a line of cancer-resistant mice leads him to believe that BCG activates granulocytes that kill cancer cells. He has shown that some healthy humans resistant mice leads him to believe that BCG activates granulocytes that kill cancer cells. He has shown that some healthy humans possess the cancer-killing activity observed in the mice.

For the clinical study, an assay developed by Cui will be used to measure the cancer-killing activity of bladder cancer patients’ granulocytes. The results will be compared with how the patients respond to BCG therapy, with the goal of verifying the assay.

In work to validate the model, five of seven animals undergoing radiation cystitis/painful bladder regenerate the model using dysplastic canine kidneys. The ultimate goal is to develop and evaluate new therapies such as cell-based therapy.

Model to Study Racial Disparity in Prostate Cancer The research team of K.C. Balaji, MD, has validated an in vitro call-clone model to study the biological basis of racial disparity in prostate cancer. Although African-American men present with higher-grade and higher-stage tumors than Caucasians, until now, few well-characterized models have been available to understand the biological basis. Balaji’s team had previously discovered the role of a gene that is abnormal in African-American men with prostate cancer. They have developed a new model that will allow them to test the role of this gene in prostate cancer.

The study demonstrates the biomarker panel is characteristically dysregulated in primary African-American cell lines similar to metastatic Caucasian cells. Therefore, the model may be used for comparative studies of potentially aggressive tumors in African-American men with prostate cancer.

As future biomarker development and validation studies establish the utility of the panel in clinical practice, “back from bench to bench” functional studies could be performed.

Viability of BCG Therapy for Prostate Cancer

Previously, the team identified a subset of patients with low bladder capacity who had an up-regulation of pro-inflammatory transcripts and a down-regulation of anti-inflammatory transcripts in bladder tissue. To evaluate the clinical correlation between bladder capacity and lower urinary tract symptoms, as well as non-urological symptoms and syndromes, the team performed a chart review of all patients in their study registry.

The analysis, involving data from 145 women with a diagnosis of IC/BPS who had undergone hydrodistention, showed there was a significant age-adjusted inverse correlation between bladder capacity and three of the measured variables: (1) urinary frequency, (2) depression and (3) IBS. Cystoscopic findings suggested more severe disease in the low capacity (<400mL) group.

In addition to the ongoing gene expression research, Wake Forest Baptist is one of several new ancillary sites selected in 2016 to perform a pilot study as part of the Multidisciplinary Approach in prostate cancer. The work demonstrated that PKD1 is down-regulated in advanced prostate cancer, leading to the conclusion that loss of PKD1 in the prostate is a late event and a marker of aggressive disease. The current research involved generating a multiplex biomarker panel that could portend progression in men with prostate cancer. The team then explored whether the panel could be used to study the biological basis of aggressive phenotype in men with prostate cancer.

The device continues to show positive results in men with obstructive prostate cancer caused by a non-muscle invasive bladder cancer after BCG failure (the BOND2 study). The study is enrolling patients who failed BCG therapy and refused cystectomy.

Daily Enemas Superior to Traditional Therapies for Nonneurogenic Pediatric Overactive Bladder

This prospective, controlled trial of 60 children with non-neurogenic overactive bladder (OAB) evaluated the efficacy of treatment with daily enemas and osmotic laxatives. Forty control patients were treated with standard therapies, including timed voiding, constipation treatment with osmotic laxatives, anticholinergics and biofeedback physical therapy.

On assessment of improvement of OAB symptoms, only 30 percent of the traditionally treated patients’ parents reported resolution of symptoms at three months, compared to 85 percent of enema patients. At the onset of the study, the average pediatric voiding dysfunction score of all patients was 1.4. On follow-up, average scores for traditionally treated patients were 12 and enema-treated patients were 4.

This study demonstrates that daily enema therapy is superior to traditional methods for the treatment of OAB. The study authors conclude that when children’s symptoms do not resolve with traditional therapy, it may be due to undiagnosed and inadequate treatment regimens.

(Submitted for publication.)
Early Fertility Preservation Program for Klinefelter Patients
Stanley Kogan, MD, and Hooman Sadri-Ardekani, MD, PhD

Klinefelter syndrome (KS, XYy or variant karyotypes) is a common cause of male infertility and occurs with a significant frequency (1:500-750 male births). Boys with this condition appear phenotypically normal at birth, but peri-pubertally, the testes undergo growth arrest, atrophy and progressive fibrosis, ultimately resulting in sub-fertility in up to 90 percent and sterility in 70 percent as adults. Recent research in this condition has indicated that the testes are functional through the time of peri-puberty, offering a “safe window” before deterioration onset occurs.

Testis tissue preservation by obtaining a biopsy to store spermatogonial stem cells (SSC) and subsequent transplantation back to the sterile Klinefelter patient or in vitro maturation of stored SSC offers a potential cure for later infertility. Though similar techniques of banking and transplantation have proven successful in several animal models, SSC transplantation back in humans has not yet been done since this technique is new and children with various causes of potential future infertility/sterility (i.e., bilateral cryptorchidism, gonadotoxic treatments for cancer, etc.) have not as yet aged to the point of establishing their fertility status.

At Wake Forest Baptist, an active multidisciplinary clinical and research program has been established for children at increased risk for potential future infertility. Central to the clinical arm is a Institutional Review Board (IRB)-approved program for testicular tissue banking and cryopreservation of SSC for children at high risk for infertility, including boys with Klinefelter syndrome. For boys at increased risk for testis deterioration and damage, a single-encounter, complete fertility preservation evaluation and treatment program has been initiated. This program offers penile vibration stimulation, electroejaculation and micro-testicular sperm extraction. In addition, drawing on the urological ultrasound expertise in our group, coordinated by Daniel Rukstalis, MD, we are assessing the use of high-resolution ultrasound elastography as a predictor of early testis fibrotic deterioration in these children who are at increased risk for later infertility.

Along with these clinical undertakings, the Male Fertility Research group at the Wake Forest Institute for Regenerative Medicine is conducting basic research to characterize the growth characteristics of Klinefelter testes and SSC and attempting to determine the natural history and causes of the spontaneous deterioration that occurs. Going forward, the main challenges are to learn why the Klinefelter tests fails, whether interventions such as pre-failure banking of SSC are confirmed as useful, and the optimum timing for intervention if proven clinically useful.

For more information and patient referral, contact Dr. H. Sadri-Ardekani at 336-713-1493 (leave a message for callback) or email fertilitystudy@wakehealth.edu.

Congratulations
Gopal Badlani, MD, received the highest award given by the Medical Council of India, the Dr. B.C. Roy National Award, to recognize his service in the field of socio-medicai relief. Badlani serves as a volunteer physician and brought together two organizations in a project to care for the underserved in India, which resulted in more than 6,000 people receiving urologic care over the past 15 years. Badlani also received the 2016 Most Distinguished Physician Award from the Association of Physicians of Indian Origin. This award is given to a physician whose work has had significant impact on science, innovations in patient care that have had widespread impact, or health-related community service that has served humanity at large.

Robert Evans, MD, was named “2015 Doctor of the Year” as part of an IC Awareness Month campaign conducted by the International Cystitis Society. According to the society, “the comments shared about his treatment empathy the dignity and compassion that he and his team show to the patients struggling with IC and pelvic pain. They are an absolute treasure to their patients and the IC community as a whole…. It’s not unusual for patients to fly from across the country (and world) for a consultation.”

Wake Forest Baptist Among First to Offer New Treatment
Wake Forest Baptist Urology was the first medical practice in North Carolina—and the 4th in the U.S.—to offer a woman a new, non-surgical treatment for accidental bowel leakage. This devastating condition is associated with a profound negative impact on quality of life.

The vaginal bowel control device was previously offered only through research studies. The system has a dynamic balloon mechanism that externally compresses the rectum to achieve continence. Of participants successfully fitted with the device, 80 percent achieved treatment success, defined as a greater than 50 percent reduction in fecal incontinence episodes. Catherine Matthews, MD, was part of the clinical study that evaluated the insert prior to approval by the U.S. Food and Drug Administration. About 45 percent of study participants were unable to enter the treatment phase as device fitting was not successful.

Ashok Hemal, MD, received the 2016 Sushruta Award from the Indian American Urological Association (IAUA). This annual award is given to a physician who has contributed to the field of medicine or performed noteworthy charitable work. IAUA, an affiliate organization of the American Urological Association, promotes interaction among practicing urologists and affiliated scientists of Indian origin in the United States.

Catherine Matthews, MD, was one of three “star” surgeons selected to participate in “Operating with the Stars” during the 45th Congress of Advancing Minimally Invasive Gynecology Worldwide.

Ryan Terlecki, MD, won two “Best Abstracts” at the 2015 Sexual Medicine Society of North America Annual Meeting: “Development of gene therapy for erectile dysfunction: delivery to corpus cavernosum using viral vectors” and “Engineering of corporal tissue constructs using non-human primate and human corpus cavernosal smooth muscle and endothelial cells for clinical applications.” He was also named “2016 Best Reviewer” by the Journal of Urology.

Matthews evaluated the clinical characteristics associated with device fitting in women with moderate to severe fecal incontinence. The study involved 110 women, ages 19-75, at six clinical sites in the U.S. Multivariate, logistic regression analysis revealed that previous prolapse surgery and shorter vaginal length were independently associated with unsuccessful fitting of the device.

Women who had not undergone previous prolapse surgery had 4.7 times the odds of a successful fit. Also, for every additional centimeter of vaginal length, women had 1.49 times the chance of a successful fit. The findings may be used to inform patients on the expectation of a successful fitting.

Anthony Atala, MD, FACS, professor and chair, is editor-in-chief of the journal, Science Translational Medicine. He is a past recipient of the Ramon y Cajal Award from the AUA and the Banning Medal from the American Association of Genitourinary Surgeons for his contributions to the field of urology. He is a member of the Institute of Medicine and is one of 98 innovators named a charter member of the National Academy of Inventors. Atala directs a team of researchers at the Wake Forest Institute for Regenerative Medicine, which works to engineer replacement tissues and organs for more than 30 different areas of the body. He serves on the American College of Surgeons Board of Regents.

Ronald L. Davis, MD, MBA, FACS, professor of urology and obstetrics/gynecology and vice chair for urology clinical affairs, directs Female Pelvic Health Services, a collaboration with Obstetrics and Gynecology. His NIH-funded research focuses on urinary incontinence. Davis is currently serving a two-year term as chair of the annual meeting of The Society of International Urology and in 2017 will assume the role of secretary of the American Association of Genitourinary Surgeons. Davis received several prestigious awards in 2016 (see page 5). He is a past board member of the National Institute of Diabetes and Digestive and Kidney Diseases. He co-edits the 4th edition of Smith’s Textbook of Endourology and serves as editor-in-chief of the Endourological Society.

K.C. Balaji, MD, professor, specializes in prostate and kidney cancer. He federally funded basic science research focuses on cell signaling and stem cells in prostate cancer. In addition, his laboratory works on cancer biology, transplant nephrology, and health disparity in prostate cancer, and he serves as a study section reviewer for the Department of Defense Prostate Cancer Research Program and on the editorial committee for the basic science section of Journal of Urology. He is the principal investigator on several Wake Forest Baptist Comprehensive Cancer Center clinical trials and has organized an active genitourinary clinical trial working group at the Medical Center.

Robert J. Evans III, MD, FACS, associate professor, directs the department’s clinical operations. He specializes in pelvic pain syndrome and serves on the medical advisory boards of the International Cystitis (IC) Association and the Intestinal Cystitis Network. He is involved in several clinical trials evaluating new treatments for painful bladder syndromes, as well as directing a study to determine the optimum injection site for botulinum toxin to treat the condition. In addition, he is part of a genomics study looking at potential differences in subclinical conditions that the American Urological Care Foundation to provide oversight on patient education materials related to bladder pain.

Jorge Gutierrez-Aceves, MD, professor, heads the department’s endourology and stone disease program. He is an assistant editor of the Journal of Endourology and is editor of the Spanish edition of the AUA News. He is a member and honorary member of various urological associations, including the American Association of Genitourinary Surgeons. He has served on the board of directors of the Endourological Society. Gutierrez co-directs the fellowship program on Endourology and Laparoscopic/Robotic Surgery at Wake Forest Baptist. He is General Secretary of the Confederacion America de Urologia, a Latin-American urological association with more than 10,000 members in 24 Spanish- and Portuguese-speaking countries.

Ashok K. Hemal, MD, MCh, FACS, professor and director of the Robotic and Minimally Invasive Urologic Surgery Program, specializes in uro-oncology, robotic and laparoscopic surgeries. He is principal or co-investigator on several research projects and is well known internationally for his pioneering work in minimally invasive surgery. He has edited several books and more than 350 scientific papers in peer-reviewed journals. He is invited as a visitor professor to deliver lectures and perform live surgeries during major conferences around the world. He has been the recipient of many academic distinctions and awards. In 2016, he received the American Urological Association’s Shands Alumni Award from the Indian American Urological Association. He currently serves as president of the Society of Urologic Robotic Surgeons.

Steve Hodges, MD, associate professor, specializes in pediatric urology. His research interests include the prevention of luminal stricture and scar disease throughout the urinary tract and body, and dysfunctional elimination. He is an associate editor of the Scientific World Journal, and wave length of the Indian Journal of Urology and BMC Urology. Multiple new treatments developed by Hodges have been licensed to startup companies, including drug-coated balloons to prevent or treat urethral strictures. A clinical trial to evaluate the technology is currently under way. He has co-authored a book for consumers on toilet training and voiding dysfunction as well as a book for children. He developed a disposable wipe designed to prevent vulvitis and urinary tract infections in girls.

Stuart Howards, MD, FACS, professor, is a nationally recognized expert in urologic microsurgery for vasectomy repair, vasectomy reversion and sperm retrieval. Howards has edited four editions of Infertility in the Male and has performed more than 1,500 vasectomy reversals. He serves on the executive committee of the Society of Reproductive Medicine. Howards served as section editor of the American Journal of Urology for 15 years, and as the AUA’s associate editor. He served as chairman of the N.C. Chapter of the American Urological Association for 15 years. He serves as a voting member of the AUA’s Legal Action Committee and is appointed to the AUA State Advocacy Board. He is a board member of the N.C. Urology Society and is the unaffiliated board member at the N.C. Chapter of the American College of Surgeons.

Robert K. Moore, MD, clinical associate professor, specializes in endourology and minimally invasive techniques to treat urologic cancers and kidney stones at the Veterans Affairs Medical Center in Salisbury, N.C. He is also an urologic resident site director at the VA. Moore is a worldwide expert in minimally invasive urologic surgery and has performed more than 2,000 Genitourinary Surgeons Kayes Medal for “outstanding contributions in the advancement of urology.”

John D. McConnell, MD, FACS, chief executive officer of Wake Forest Baptist Medical Center, is a noted urologist and international authority on prostate disease who remains clinically active. He received the American Association of Genitourinary Surgeons’ Banning Medal for his contributions to the field of urology and is a member of the Institute of Medicine. As CEO, a noted achievement has been leading Wake Forest Baptist to a legally integrated governance and management structure, the first time in the institution’s history that its components operated under a legally integrated structure.

Majid Mirzaeizadeh, MD, assistant professor, focuses on female urology and incontinence, stone diseases, infections, prostate diseases and kidney cancer. He is also a principal investigator on several research projects and is a co-investigator on several research projects and is a co-investigator on several research projects. He has published over 100 articles in peer-reviewed journals. He is the inventor of an incremental syringe designed to deliver multiple-injection products without requiring close visual monitoring of the injection site. He is also a national expert in the management of male secondary infertility.

Daniel Rokitski, MD, PhD, professor, directs the urology residency program and is board certified in urology and pediatrics. He specializes in minimally invasive urologic and pediatric surgery. He is a recognized leader in the field of pediatric urology. Rokitski’s expertise involves clarifying the importance of genetics and endocrine studies in the evaluation of male factor treatment with novel assisted reproductive technology. He directs a national comprehensive referral program that aims to prevent infertility in patients of all ages due to cancer, Klinefelter syndrome, spinal cord injury, diabetes and multiple sclerosis. He also directs a male fertility research program at the Wake Forest Institute for Reproductive Medicine.

Allison J. Stubbs, MD, clinical associate professor, specializes in male infertility, treatment with novel assisted reproductive technology. He directs a national comprehensive referral program that aims to prevent infertility in patients of all ages due to cancer, Klinefelter syndrome, spinal cord injury, diabetes and multiple sclerosis. He also directs a male fertility research program at the Wake Forest Institute for Reproductive Medicine.

Ryan Terlecki, MD, FACS, associate professor, is director of the Men’s Health Clinic, the Urologic Cancer Surveillance Program and the department’s fellowship in urologic reconstruction, prosthetic urology and male incontinence. He is a recognized leader in urinary reconstruction, Peyronie’s disease and prosthetic surgery for erectile dysfunction and male stress urinary incontinence. In addition, he is an investigator in novel therapeutics that use cell-based and tissue-based technologies to treat urethral stricture, sexual dysfunction, and male incontinence. Terlecki serves as associate editor of BMC Urology and is a reviewer for numerous journals and national guidelines. He is the Young Fellows Association liaison representative to the American College of Surgeons’ Health Policy Advisory Council.
Wake Forest Baptist Urology offers four fellowship programs rich in both clinical care and academic research. As part of a high-volume tertiary referral center, the department is a leading program for index cases for both adult and pediatric urology. Training advantages also include a surgical skills learning center with mock ORs and simulated patients.

**Endourology/Robotic Surgery:** Two-year program offering an intensive clinical and research experience to prepare fellows for a career in academic medicine. Fellows obtain advanced experience in all aspects of endourologic, laparoscopic and robotic surgery, and gain research experience, including the option for a master’s degree. Accredited by the Endourological Society.

**Laparoscopic/Robotic Surgery:** One-year fellowship designed to prepare fellows for a career in robotic urologic surgery, laparoscopic and urology and urologic oncology. Fellows participate in a wide range of urologic procedures, from radical prostatectomy and cystectomy to partial nephrectomy and reconstructive procedures. A variety of research opportunities are available. Accredited by the Endourological Society.

**Female Pelvic Medicine and Reconstructive Surgery:** Two-year program for urology physicians versus a three-year program for Ob/Gyn graduates. The program includes 12 months of research. The curriculum is designed to comprehensively train pelvic surgeons to develop clinical independence through mastery of a broad range of diagnostic and surgical techniques. Accredited by ACGME.

**Genitourinary Reconstructive Surgery:** One-year clinical program in male genitourinary reconstructive surgery, prosthetic urology, and infertility. Fellows are exposed to the most up-to-date surgical techniques to equip them to serve as an educator and leader in the field. Fellows can participate in research at the Wake Forest Institute for Regenerative Medicine. Verified by the Society of Genitourinary Reconstructive Surgeons.