NYU Langone Health

Urology

2018 Year in Review

MESSAGE FROM THE CHAIR

Over the past year, our urology faculty have made great strides in understanding the mechanisms underlying urologic diseases and advancing treatments.

Among our many bench-to-bedside advances, our department is at the forefront of exploring new options for the screening, detection, and treatment of prostate cancer. Following one of the largest studies of its kind, our researchers report on the importance of conservative management as a strategy for low-risk disease, and we look at our recent experience performing focal ablation as well as radical prostatectomy. We are also testing novel compounds against prostate cancer cells, including a new type of molecule that blocks the action of genes involved in treatment-resistant prostate cancer. Other advances include innovations in reconstructive surgery as well as novel treatments for voiding dysfunction. Read on to learn more about our achievements and their potential impact on patient care.

HERBERT LEPOR, MD

Professor, Department of Urology
Professor, Department of Biochemistry and Molecular Pharmacology
Martin Spatz Chair, Department of Urology
Chief, Urology

CAMPUS TRANSFORMATION

In 2018, NYU Langone Health opened a new, 830,000 square foot inpatient facility, the **Helen L. and Martin S. Kimmel Pavilion**, featuring 374 exclusively single-bedded rooms, an outdoor terrace, and 30 operating rooms and image-guided labs.

(Photo credit: Jeff Goldberg)

DEPARTMENT OF UROLOGY

Top 10

IN THE NATION IN UROLOGY

U.S. News & World Report's "Best Hospitals 2018—19"

Prioritizing Detection

& FOCAL ABLATION OF CLINICALLY SIGNIFICANT PROSTATE CANCER

while helping preserve men's quality of life

1 in 8

PRACTICING U.S. UROLOGISTS

have attended NYU Langone for postgraduate education

Diverse

PRACTICE SETTINGS

public, private, and VA health systems

P01

NCI PROGRAM PROJECT GRANT

with a focus on molecular tumorigenesis of bladder cancer

Fewer Veterans Opting for Aggressive Treatment of Low-Risk Prostate Cancer

A recent study led by NYU School of Medicine and Manhattan VA NY Harbor Healthcare System researchers reveals that conservative management has become the preferred management option for U.S. veterans with low-risk prostate cancer.

Nataliya Byrne; Stacy Loeb, MD, MSc; and Dawn Walter, MPH (Photo credit: Juliana Thomas Photography)

The findings signal a reversal after decades of overtreatment for low-grade tumors and suggest that more physicians are heeding best practice guidelines.

MORE GUIDELINES-CONCORDANT CARE

The investigation was led by Stacy Loeb, MD, MSc, assistant professor of urology and population health at NYU Langone Health, an attending urologist at the Manhattan VA, and a member of Perlmutter Cancer Center at NYU Langone Health. Her team found that patients with low-grade tumors were far less likely to pursue aggressive treatment in 2015 than in 2005—a period when prostate-specific antigen (PSA) testing came under increasing criticism for inducing over-diagnosis leading to unnecessary treatments. Findings were published online in the May 2018 issue of *Journal of the American Medical Association*.

The study, one of the largest to date examining U.S. treatment patterns for low-risk disease, was based on an analysis of more than 125,000 patient records contained in the VA's Central Data Warehouse. Patients had a mean age of 64 and mean PSA of 5.4 ng/mL.

CONSERVATIVE MANAGEMENT INCREASING IN ALL AGE GROUPS

Researchers noted a substantial rise in the use of active surveillance during the study period across all age groups. During the study period, the percentage of men younger than age 65 who opted for watchful waiting or active surveillance over surgery jumped from 27 percent to 72 percent, with a similar increase seen among older patients.

Associated with greater odds of conservative management were increasing age, black race, unmarried status, higher PSA, increasing comorbidity, and geographic region. Among men choosing conservative management, those older than 75 years, with higher PSA scores, and with greater comorbidity were more likely to receive watchful waiting as opposed to active surveillance.

> "This marks a historic reversal, at least at the VA, in the decades-long overtreatment of men with prostate cancers least likely to cause harm. It brings their care more in line with the latest best practice guidelines, such as those of the American Society of Clinical Oncology and American Urological Association, which discourage aggressive therapy for low-grade tumors."
>
> **—Stacy Loeb, MD, MSc**

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Fewer Veterans Opting for Aggressive Treatment of Low-Risk Prostate Cancer

VA'S SUCCESS MIRRORS SWEDEN'S MODEL OF HIGH-QUALITY, VALUE-BASED CARE

In light of published data, the findings indicate that overtreatment has become less of a problem at the VA than in other U.S. healthcare settings, researchers noted. For example, only 32 percent of patients received conservative management in the Surveillance, Epidemiology, and End Results (SEER)-Medicare-linked database from 2010–2011. Similarly, 2010–2013 data from a registry of 45 community-based urology practices show that 40 percent of patients were managed conservatively.

The VA's success in improving the standard of care for low-risk prostate cancer patients is comparable to data from countries known for providing high-quality, value-based care, said Dr. Loeb. Sweden, for example, reported 74 percent of patients undergoing active surveillance in 2014.

Despite the trend toward best practice adherence, certain circumstances may lead patients to prefer immediate treatment, such as an infection following the initial biopsy, says Dr. Loeb. The important point, she stresses, is for physicians and patients to carefully review all options and risks upfront and engage in shared decision-making.

"The main conclusion to be drawn from the data is that most veterans with low-risk prostate cancer are now adopting conservative management, and other American men might follow suit if counseled on the potential benefits," says Dr. Loeb. With funding from the Prostate Cancer Foundation, Dr. Loeb and her team are creating additional tools and online education materials to improve active surveillance.

(Photo credit: Inti St Clair via Getty Images)

Prostate Cancer Foundation 2018 Young Investigator Awards

Danil H. Makarov, MD
assistant professor of urology and population health and director of surgical research, Department of Population Health:

Exploring Contextual Factors Associated With Effectiveness of a Physician-Centered Behavioral Intervention To De-Implement Guideline-Discordant Prostate Cancer Imaging

Danil V. Makarov, MD

David R. Wise, MD, PhD
assistant professor of medicine and urology:

Overcoming Immune Evasion in Androgen Receptor-Independent Prostate Cancer through Targeting Dickkopf-1 (DKK1)

David R. Wise, MD (Photo credit: Juliana Thomas)

Funding/Support: Dr. Loeb's JAMA study was supported by the Edward Blank and Sharon Cosloy Blank Family Foundation, the Gertrude and Louis Feil Family; and by grants DOH01-C30697GG-3450000 from the New York State Department of Health, P30CA016087 from the Laura and Isaac Perlmutter Cancer Center at NYU Langone, the Prostate Cancer Foundation, K07CA178258 from the National Institutes of Health (NIH) (Dr. Loeb), and CDA11-257 and CDP11-254 from the US Department of Veterans Affairs (Dr. Makarov).

Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr. Loeb reported consulting for Lilly, MDxHealth, GenomeDx, and General Electric, and receiving personal fees from Astellas, Sanofi, Minomic, and Boehringer Ingelheim. Dr. Makarov reported consulting for the U.S. Food and Drug Administration. Dr. Lepor reported previously holding shares in SonaCare Medical and receiving research support from and serving on the advisory board for Genomic Health. No other disclosures were reported.

Promising Options for Reducing Urinary Tract Symptoms in Complex Patient Populations

NYU Langone urologists continue to test promising new treatments to alleviate bothersome urinary conditions in complex patient populations, such as elderly patients with medical comorbidities and patients with Parkinson's disease.

Benjamin M. Brucker, MD
(Photo credit: Karsten Moran)

"The treatment paradigm we're currently following isn't very effective; as a medical community, we could be doing a better job with the management of these patients—and now we have the needed insight to effectively and safely get them the deep, restorative sleep they need."

Benjamin M. Brucker, MD

Findings from several recent studies have the potential to significantly improve quality of life for those struggling with overactive bladder (OAB), the urgent and frequent need to pass urine, and nocturia, which is excessive nighttime urination.

NASAL SPRAY PROVIDES RELIEF FOR NOCTURIA

One published study examined the effectiveness of AV002, a recently approved emulsified vasopressin nasal spray, in treating elderly patients with nocturia due to nocturnal polyuria. Benjamin M. Brucker, MD, associate professor of urology and obstetrics and gynecology, director of female pelvic medicine and reconstructive surgery and neuro-urology, and director of the Female Pelvic Medicine Fellowship Program, reported results during a late-breaking session of the 2018 meeting of the American Urological Association and as part of a team at the International Continence Society 2018 annual meeting in Philadelphia.

Men and women with nocturia awaken multiple times during the night to urinate, interfering with sleep patterns and often triggering associated problems, such as cognitive decline, depression, and a weakened immune system. Although anticholinergics are currently the standard treatment, previous research by Dr. Brucker and his colleagues demonstrated that AV002 is faster acting and more effective.

In this study, Dr. Brucker and colleagues randomized two groups of adults aged 65 and older and 75 and older to receive either AV002 (1.66 mcg or 0.83 mcg) or placebo for 12 weeks. To assess the medication's impact on sleep quality, researchers measured patients' first uninterrupted sleep period (FUSP), defined as the time from bedtime to first voiding, and the percentage of nights with no more than one nocturic episode. Of note, the patients in both groups had multiple comorbidities and were on several medications (median=7).

The baseline FUSP was 2.4 hours for both dosage groups and placebo. Both ≥65y and ≥75y patients treated with AV002 demonstrated significant improvement in duration of FUSP and percentage of nights with ≤1 nocturic void. For both age groups, the mean first uninterrupted sleep period after treatment was greater than four hours for the 1.66 mcg group and approximately four hours for the 0.83 mcg group.

In addition, AV002 had a side-effect profile similar to that of placebo and was associated with a very low rate of hyponatremia, despite this elderly population's generally higher risk for side effects.

The findings suggest that physicians should consider AV002 as an alternative to anticholinergics in patients who experience two or more nocturic episodes, says Dr. Brucker. Since nocturia is more common in older patients, these robust data give clinicians a new tool to manage this at-risk population, he adds.

New Tool to Manage Nocturia in At-Risk Population

	AV002: 1.66 mcg group	AV002: 0.83 mcg group
Baseline First Uninterrupted Sleep Period	**2.4 hours**	**2.4 hours**
Age greater than or equal to 65	>4 hours	Approximately 4 hours
Age greater than or equal to 75	>4 hours	Approximately 4 hours

Promising Options for Reducing Urinary Tract Symptoms in Complex Patient Populations

OPTIONS FOR OVERACTIVE BLADDER IN PATIENTS WITH PARKINSON'S DISEASE

Dr. Brucker also led two retrospective studies investigating alternative treatments for OAB in patients with Parkinson's disease. Patients with overactive bladder often have distressing urinary incontinence. When patients have a neurological basis for their bladder dysfunction, the efficacy of available treatments can be difficult to assess.

To shed light on the efficacy and safety of potential treatments, Dr. Brucker and a team of researchers including Nirit Rosenblum, MD, clinical associate professor of urology and obstetrics and gynecology, and co-director of the Female Pelvic Medicine Fellowship Program, examined two therapies that have been used in OAB patients without Parkinson's disease; one study investigated mirabegron, a novel Beta adrenoceptor agonist approved for OAB in 2012; the other examined onabotulinum toxin A injections (Botox; Allergan). While both treatments have been shown to be safe and effective for OAB, anticholinergic drugs—which increase the risk of cognitive dysfunction and adverse events—remain the standard of care for patients with Parkinson's disease, due to lack of clinical studies.

In the first study, investigators examined records of 50 Parkinson's patients who received daily doses of mirabegron between 2012 and 2017. After six weeks of treatment, 50 percent of patients experienced improvement, and 11 percent reported complete resolution of their OAB symptoms. The therapy was well tolerated, and median time to discontinuation (17 months) was longer than that observed in other OAB patients.

In the onabotulinum toxin A study, researchers analyzed outcomes for a cohort of Parkinson's patients who underwent 100U injections between 2010 and 2017. Over a four week period, 79.2 percent of patients showed improved symptoms after the initial injection, increasing to 87.5 percent with repeat injection. About 12 percent of patients required clean, intermittent catheterization for urinary retention after the first injection.

The study findings were published online in May 2018 in *Neurourology and Urodynamics* and online in July 2018 in *Parkinsonism and Related Disorders*, respectively. Considering their more favorable side-effect profile compared with anticholinergics, both treatments merit further consideration as viable therapies in Parkinson's patients with OAB, the researchers concluded.

Nirit Rosenblum, MD

Disclosure: Dr. Brucker is an advisor and speaker for Avadel (maker of AVOO2) as well as a speaker, advisor, and investigator for Allergan (maker of BOTOX®). He is also an investigator for ISPEN (makes medication similar to Botox) and an advisor for Watkins-Conti Products, Inc. (nothing related to these studies).

Exploring New Options for Prostate Cancer Detection and Treatment

To meet the challenges of treating prostate cancer while reducing associated risks, NYU Langone continues to lead research identifying new applications for focal ablation.

Herbert Lepor, MD
(Photo credit: Karsten Moran)

James S. Wysock, MD

Focal ablation, the promising minimally invasive alternative to radical prostatectomy and radiation therapy, causes fewer treatment-related complications, and may be the optimal management choice for a select group of men with clinically localized prostate cancer.

RESEARCH HOMES IN ON OPTIMAL FOCAL ABLATION CANDIDATES

Optimal management of the spectrum of prostate cancers includes a range of options, from active surveillance to whole-gland removal. In select cases, recent research points to focal ablation (FA) as a viable alternative option that can potentially control disease while preserving the patient's quality of life, says Herbert Lepor, MD, professor of urology and biochemistry and molecular pharmacology and the Martin Spatz Chair of the Department of Urology.

The studies have found that FA not only achieves acceptable disease control in select patients, but also results in far fewer treatment-related complications, such as urinary, gastrointestinal, and sexual side effects, that frequently accompany radical prostatectomy or radiation therapy.

Selecting candidates for FA is based on detecting lesions with magnetic resonance imaging (MRI), which does not detect very small low-risk disease. However, MRI has been shown to identify the index (or most aggressive) tumor accurately in 93 percent of candidates for FA who underwent radical prostatectomy, according to one study led by Dr. Lepor. The study, presented at the American Urological Association Annual Meeting and published in the February 2018 issue of *Urology*, reported on 59 men who underwent radical prostatectomy and met the criteria for FA. Dr. Lepor found that only a small proportion of very low volume intermediate-risk cancers would have been left untreated if the men had received FA.

More recently, Dr. Lepor turned his attention to further defining oncological control following FA, an area of unmet need when it comes to evidence-based counseling for men considering FA. Dr. Lepor and his colleague James S. Wysock, MD, assistant professor of urology, acknowledged the lack of data in a comprehensive review published in the June 2018 issue of *Reviews in Urology*. "More research is needed on whether untreated disease within or beyond the ablation zone will become life-threatening over time," says Dr. Lepor.

IMPORTANCE OF FOLLOW-UP CARE CONFIRMED BY STUDY

New findings from Dr. Lepor and colleagues represent the first published data on follow-up care beyond one year in the context of FA treatment. The research, published in the June 2018 issue of *European Urology Oncology*, reports on quality of life and disease recurrence in 32 men who underwent PSA testing and MRI at six months and two years following laser FA.

At the two-year mark, MRI reliably identified recurrence of intermediate-risk disease in the ablation zone, investigators reported, providing compelling evidence that patients should undergo interval MRI and biopsy upon positive findings. The procedure had virtually no adverse impact on urinary or sexual function.

It can be challenging to define what constitutes significant or aggressive disease following FA, notes Dr. Lepor. For this study, investigators targeted at least four biopsies in and around the ablation zone and assigned risk based on National Comprehensive Cancer Network guidelines, as follows:

- Intermediate risk: Gleason pattern 4
- Low risk: Gleason 6 with >50 percent core involvement
- Very low risk: Gleason 6 with <50 percent core involvement and fewer than three positive cores.

In the study, eight patients with positive MRI were found to have cancer in the ablation zone. Of these, six were intermediate-, one low-, and one very low-risk. In patients with negative MRI findings, intermediate-risk disease was rarely detected, notes Dr. Lepor.

"The decision to perform biopsy in MRI-negative patients should be guided by whether finding low-risk disease would influence management," he concludes.

CONCLUSIONS YIELD NEW QUESTIONS

While more research is needed, it's clear that ongoing monitoring and testing are essential following FA, says Dr. Lepor.

"Our study provides compelling evidence that many men with a negative biopsy at six months may develop in-field recurrences at two years," he says. "A positive MRI scan should prompt a biopsy, preferably one that is MRI-guided to the ablation zone."

The recent follow-up study also highlights the need to refine how FA is performed and how men should be followed, notes Samir S. Taneja, MD, the James M. Neissa and Janet Riha Neissa Professor of Urologic Oncology; professor of urology, radiology, and biomedical engineering; director of urologic oncology and vice chair, Department of Urology, and genitourinary oncology program leader, Perlmutter Cancer Center.

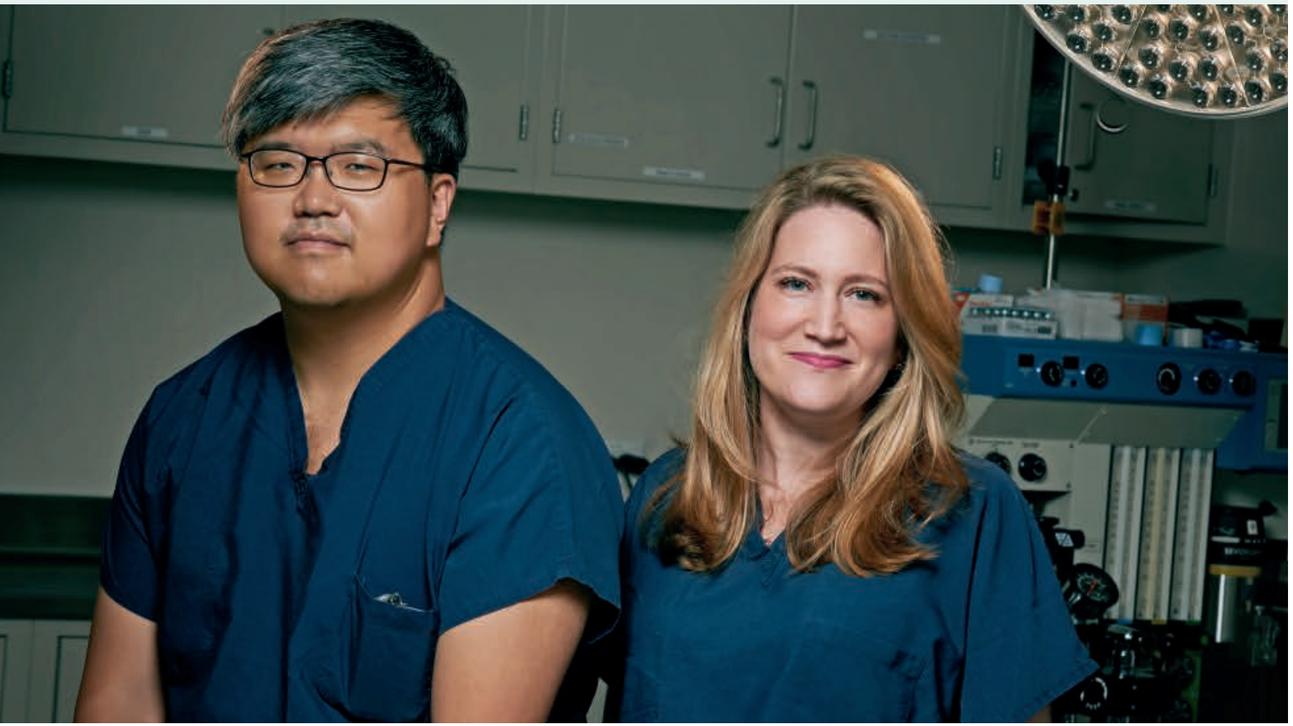
"The fact that almost 30 percent of men in our study developed intermediate-risk prostate cancer in the ablation zone within two years is disconcerting," Dr. Taneja says. "It suggests that the extent of the ablation zone or delivery of laser energy is inadequate and needs refining. This is consistent with data we have previously published demonstrating that MRI underrepresents the extent and size of many tumors, suggesting that MRI-targeted ablations must incorporate an adequate margin to ensure complete tumor destruction." To that end, NYU Langone urologists now employ cryo-ablation and high intensity focused ultrasound (HIFU) as preferred energy sources to destroy regions of the prostate harboring cancer, because they allow for reliable incorporation of wider margins around the targeted tumor.

Samir S. Taneja, MD
(Photo credit: Jonathan Kozowyk)

Disclosures: Herbert Lepor, MD is co-owner of MedReviews and has investment interests in Serenity Pharmaceuticals and UroGen Pharma. He previously had an investment interest in SonaCare Medical. Samir S. Taneja, MD is currently a consultant for Insightec, Sophiris, and Trod Medical, as well as a scientific study investigator for MDxHealth. He also receives book royalties from Elsevier. James S. Wysock, MD: is a paid speaker/consultant for Endocare Inc.; a paid speaker for Fortec Medical, Inc.; a consultant for Boston Scientific; Genomic Health Inc.; Intuitive Surgical Inc.; Precision Biopsy, Inc.; Sonacare, Inc.; Tomer Pharmaceuticals, Inc.; and United Medical Systems.

Case Study: Innovative Robotic Approach for Managing Proximal Ureteral Strictures

Urologists at NYU Langone lead the field with expertise in the use of robotic assistance during laparoscopic repair of ureteral strictures.



Lee C. Zhao, MD, and plastic surgeon Rachel Bluebond-Langner, MD (Photo credit: Sasha Nialla)

Lee C. Zhao, MD, first described the technique of robotic ureteroplasty with buccal mucosal graft for management of a proximal ureteral stricture in the September 2015 issue of *Urology*.

In a current case, a 40-year-old male patient was referred to NYU Langone after undergoing multiple procedures that failed to resolve a 4 cm proximal ureteral stricture that had developed as a result of treatment with ureteroscopy and laser lithotripsy for an impacted ureteral stone. Before seeking treatment at NYU Langone, the patient underwent ureteral dilation, endoureterotomy, and placement of a stent. After stent removal, he developed pain and hydronephrosis, necessitating nephrostomy placement at the outside institution. Using robot-assisted laparoscopy, NYU Langone urologists successfully achieved ureteral reconstruction with a buccal mucosa onlay graft.

LOCATION AND EXTENT OF STRICTURE GUIDE SURGICAL MANAGEMENT

"At NYU Langone, we typically perform ureteroneocystostomy in patients who have distal ureteral strictures," explains Lee C. Zhao, MD, MS, assistant professor of urology, director of male reconstructive surgery, and co-director, Transgender Reconstructive Surgery. "If the patient has a mid-ureteral stricture with sufficient bladder capacity, a Boari flap can be utilized. In patients with proximal ureteral strictures where a direct connection from the ureter to the renal pelvis is possible, pyeloplasty is performed," Dr. Zhao continues.

"Onlay of buccal mucosa or an appendix flap can be used for ureteral reconstruction in large proximal strictures. If a long segment of the ureter is missing, ileal ureter transposition is a potential option, but potential bowel complications include ileus and metabolic acidosis," he says. "Autotransplantation may provide a solution as a last resort, although it is associated with the risk of vascular injury to the recipient vessels."

> "70% of ureteral strictures are benign and iatrogenic. Most benign strictures are related to ureteral calculi."
>
> **—Lee C. Zhao, MD**

Total Healthcare for Individuals Seeking Gender-Affirming Procedures

NYU Langone Health is at the forefront of research and innovation in gender-affirming procedures, conducting studies to improve patient outcomes and satisfaction and to contribute to the total healthcare of transgender individuals. NYU Langone's multi-disciplinary team provides medical services for transgender men, women, and adolescents, including surgery, hormone therapy, reproductive health services, and mental health services.

Lee C. Zhao, MD, MS, assistant professor of urology and director of Male Reconstructive Surgery, who came to NYU Langone in 2013, has pioneered the use of robotic techniques to make transgender procedures safer, faster, and less invasive. Dr. Zhao often collaborates with Rachel Bluebond-Langner, MD, the Laura and Isaac Perlmutter Associate Professor of Reconstructive Plastic Surgery, who joined NYU Langone's Hansjörg Wyss Department of Plastic Surgery from the University of Maryland School of Medicine. Dr. Zhao and Dr. Bluebond-Langner are part of a growing team of specialists at NYU Langone who care for transgender patients. Together, they have established one of the country's only dual-surgeon, cross-specialty programs that performs robotic "bottom" genital surgery for vaginoplasty and phalloplasty, which many experts agree presents safer and more effective results.

NYU Langone's main campus and NYU Langone Hospital—Brooklyn, both part of NYU Langone Health, have been recognized as leaders in lesbian, gay, bisexual, transgender, and queer (LGBTQ) healthcare equality by the Human Rights Campaign Foundation in its 2018 Healthcare Equality Index.

Case Study: Innovative Robotic Approach for Managing Proximal Ureteral Strictures

Preoperative anatomic assessment of the stricture includes evaluation of the degree of obstruction, relative renal function, and surrounding vascular anatomy. In this case, antegrade and retrograde pyelograms were performed to delineate the patient's 4 cm proximal stricture (Figure 1).

"A stent may obscure the delineation between the normal ureteral segment and the stricture," Dr. Zhao explains, "so we remove the ureteral stent before reconstruction, to allow the stricture to mature. If the patient is dependent upon a ureteral stent, we place a nephrostomy tube before stent removal."

INTRAOPERATIVE IDENTIFICATION OF DISEASED TISSUE IS CRITICAL TO SUCCESS

After transport to the OR, the patient was placed in the flank position with the ureter exposed. Four robotic trocars were placed. Intraoperative ureteroscopy with FireFly® fluorescence imaging was performed to identify the location of the stricture (Figure 2). An incision was performed on the anterior surface of the narrowed segment of the ureter until a 4 cm opening was achieved (Figure 3).

BUCCAL MUCOSA TISSUE CHARACTERISTICS ARE IDEAL FOR URINARY TRACT RECONSTRUCTION

After measurement of the defect, a buccal mucosal graft of appropriate size was harvested from the cheek and passed into the abdomen. Buccal mucosa has a thick epithelium, and the lamina propria is highly vascularized, making it a good choice for repair of ureteral strictures.

The graft was sutured on as an onlay until the ureteral defect was covered entirely (Figure 4). An omental flap, which had been mobilized during the initial dissection, was then secured around the anastomosis at the psoas muscle and sutured to the graft to provide vascularity.

A PROMISING ALTERNATIVE TREATMENT OPTION WITH A SUCCESSFUL OUTCOME

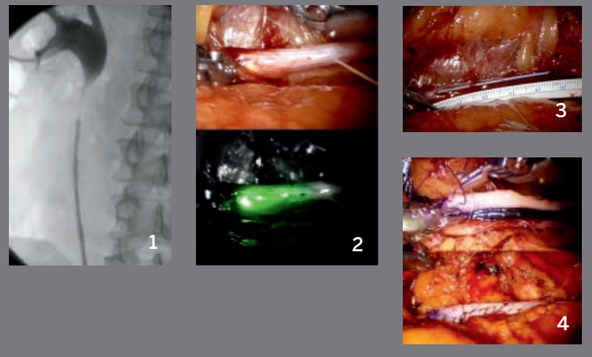
The patient was discharged on postoperative day 1, and the ureteral stent was removed after four weeks. The patient had complete resolution of flank pain. Subsequent renal ultrasound showed no hydronephrosis, and renal scan demonstrated good drainage. This case and other case reports and series demonstrate the expansion of treatment options and improved patient outcomes achieved through the use of laparoscopy with robotic assistance in the performance of challenging urologic surgeries.

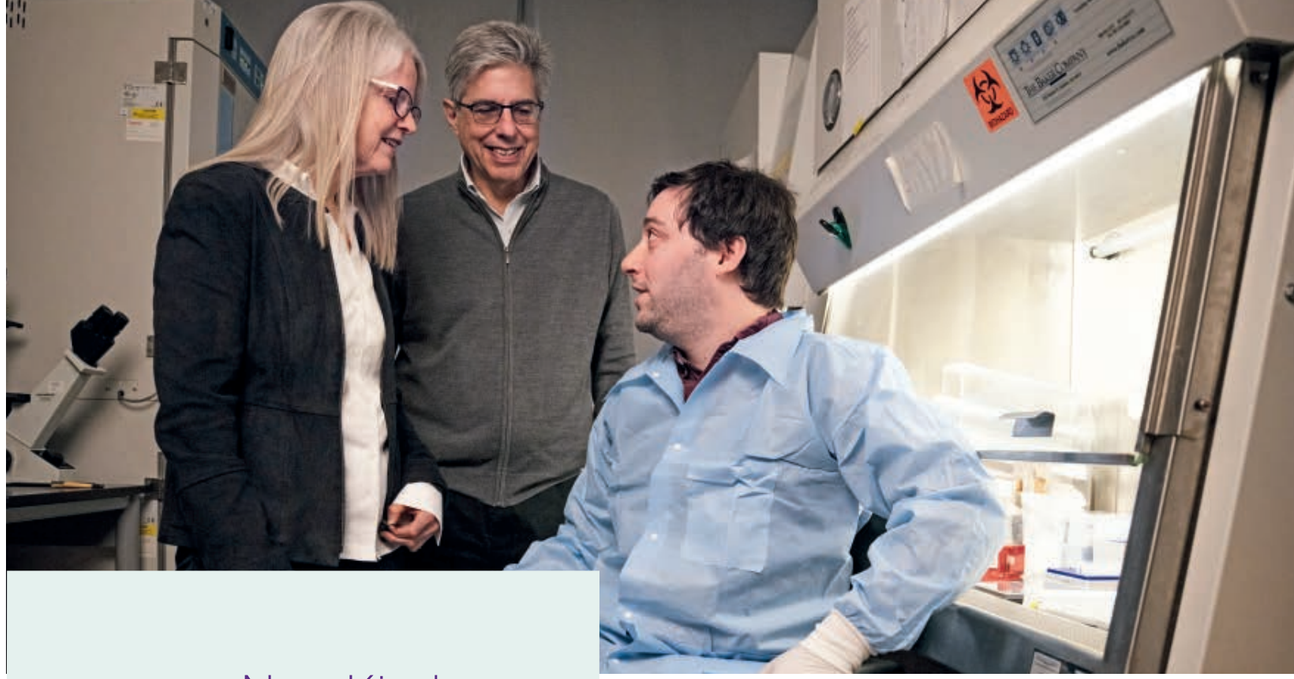
Figure 1. Antegrade and retrograde pyelogram showing a 4 cm proximal ureteral stricture.

Figure 2. Ureteroscopy performed to identify the exact location of the stricture. Turning on FireFly® fluorescence imaging mode allowed for visualizatiaon of the ureteral stricture.

Figure 3. Incision of the narrowed ureter reveals a 4 cm segment of stricture.

Figure 4. The buccal mucosa graft sutured as an onlay to reconstruct the ureteral segment.





Susan K. Logan, PhD, and colleagues Michael J. Garabedian, MD, and Jeffrey Schneider, MD/PhD Student

New Kind of Compound Shows Early Promise Against Prostate Cancer

A new type of molecule blocks the action of genes that drive the growth of therapy-resistant prostate cancer, a new study finds.

RETHINKING DRUG-LIKE MOLECULES

"Rather than continue making compounds that are just like older drugs, the focus of our work has been to rethink the definition of what a drug-like molecule can be," says corresponding author Susan K. Logan, PhD, associate professor of urology and biochemistry and molecular pharmacology, at NYU School of Medicine.

A joint research team from the School of Medicine and New York University found that their "cyclic peptoids" reduced the growth of prostate cancer cells in cultures by 95 percent compared to untreated cells. The experimental drugs also blocked a key, related growth signal in live animal tests.

"We designed our peptoids specifically to hit targets that are currently 'undruggable,' such as those causing treatment-resistant prostate cancer," adds co-senior author Kent Kirshenbaum, PhD, professor in the Department of Chemistry at New York University.

According to the team's report, published online October 2018 in *Nature Communications*, the study compounds blocked growth by interfering with the interaction between the protein beta-catenin and T-Cell Factor (TCF) transcription factors—proteins that turn on

New Kind of Compound Shows Early Promise Against Prostate Cancer

> Rather than continue making compounds that are just like older drugs, the focus of our work has been to rethink the definition of what a drug-like molecule can be."
>
> **—Susan K. Logan, PhD**

genes that make cells multiply. Although the genes are critical for early development of prostate tissue, this gene activity is normally dialed down in adulthood, unless changes re-activate it, which can lead to cancer.

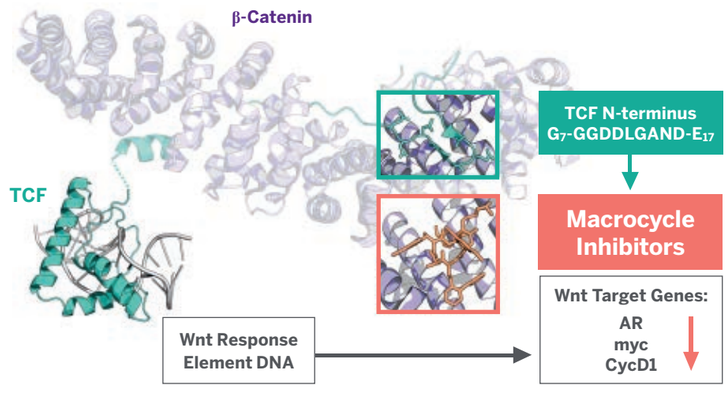
FIRST TEST

Unlike many existing drugs, the new compounds do not target androgen hormonal signals known to encourage prostate cancer. Most patients treated with anti-androgen drugs see their cancer growth resume within months, so the field has sought additional therapeutic strategies. Many efforts have focused on abnormal Wnt protein signals that occur in 20 percent of the most treatment-resistant prostate tumors, but none have made it to the clinic.

Wnts can cause the buildup of the protein beta-catenin in cell nuclei, where it turns on genes. Leading up to the new study, the research team spent years designing a new class of rugged, adjustable, protein-like compounds called peptoids that are just large enough to engage with the broad, flat surfaces used by beta catenin to interact with TCFs.

Further, the researchers knew their compound must be engineered, not just to include the right chemical components, but also to fold into a desired three-dimensional form. The researchers "stapled" together the ends of a linear peptoid molecule to form a loop-like, or cyclic, structure. This form resembled the protein hairpins that TCFs depend on to interact with beta catenin. The stapling stiffened the peptoid such that it could occupy and block the docking site that TCFs would otherwise use.

PROPOSED MECHANISM FOR TARGETING β-CATENIN



Assembling a Team to Design a New Drug Class

Susan Logan, PhD	NYU Langone Health	Corresponding author and prostate cancer expert who helped choose beta catenin as the cyclic peptoid target
Kent Kirshenbaum, PhD	New York University	Senior study author and leader of chemist team who designed the peptoids
Michael Garabedian, PhD	NYU Langone Health	Prostate cancer androgen expert and study author
Jeffrey Schneider	NYU School of Medicine MD/PhD student	First author; synthesized compounds and led experimental biologic work testing compounds against prostate cancer cells
Richard Bonneau, PhD	New York University	Computer design of the molecule and mentor
Timothy Craven, PhD	New York University	Co-first author; designed the active cyclic peptoid
Holger Knaut, PhD	NYU Langone Health	Collaborator leading the zebrafish work
Amanda Kasper, PhD	NYU Langone Health and New York University	Synthesized compound
Chi Yun, PhD	NYU Langone Health	Director, High Throughput Biology Laboratory

A more detailed attribution list is published online in the October 2018 issue of *Nature Communications*.

PREVIEWING HOW DRUG CANDIDATES MIGHT FIT INTO PROTEIN TARGETS

A new generation of computer simulation tools enabled the team to see early on how drug candidates might fit into their protein target. After this virtual testing, the team then synthesized the compounds for experiments in nutrient-filled, artificial environments called spheroids, where cancer cells grow in three dimensions (more lifelike than in two-dimensional petri dish cultures).

In these experiments, cyclic peptoids reduced treatment-resistant prostate cancer cell growth by roughly 95 percent when compared to untreated cancer cells over 22 days, which compared to just 40 percent growth reduction in cells treated with the unstapled version of the peptoid. The compounds also decreased androgen hormonal signaling, suggesting a dual anti-cancer effect, say the authors.

The researchers also wanted to show that their lead compound could block beta-catenin signals in a live animal. They chose zebrafish, in which rare genetic changes (mutations) that let beta-catenin build up are known to keep eyes from forming. In repeated experiments in fish with such mutations, the team found that their looping peptoids—by blocking overactive beta-catenin:TCF interactions similar to those affecting human prostate cancer—rescued eye development.

Furthermore, the treatment showed no toxicity in zebrafish at the rough equivalent of a dose that may work clinically in humans. Moving forward, the team will soon test their peptoids on human prostate cancer cells grown in mice. In addition, tests are planned to see if the compound can block the beta-catenin:TCF interactions known to encourage growth in colon and breast cancers.

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72
PRESENTATIONS AND ABSTRACTS
at the 2018
AUA annual meeting

16
PRESENTATIONS
at international
conferences

10+
SUBSPECIALTIES

Awards & Recognition

David S. Goldfarb, MD, holds several leadership positions in the field of nephrology. He is on the editorial board of the *Clinical Journal of the American Society of Nephrology* and a past president of the Research on Calculus Kinetics (R.O.C.K.) Society.

William C. Huang, MD, continues as co-director of the NYU Langone Robotic Surgery Center. Dr. Huang uses robotic surgical techniques in minimally invasive surgeries to remove kidney, bladder, prostate, and testicular cancers with minimal side effects and improved quality of life for patients. Dr. Huang also serves on national and international committees that publish guidelines for the management of cancers of the urinary tract.

Herbert Lepor, MD, is a co-founder and the current editor of *Reviews in Urology* and is on the editorial board of Urology.

Stacy Loeb, MD, MSc, is an Associate Editor for *BJU International*, and also serves on the editorial boards of the *Journal of Clinical Oncology, European Urology, Nature Reviews Urology* and *Reviews in Urology*. Dr. Loeb hosts the Men's Health Show on SiriusXM 110 satellite radio, and chairs the American Urological Assocation Social Media Work Group. She was also recently inducted into the Association of Academic European Urologists.

Danil V. Makarov, MD, MHS, is a member of the Society for Medical Decision Making, a diplomate of the American Board of Urology, and chair of the White Paper Committee on Implementation of Shared Decision Making into Urological Practice of the American Urological Association. He is also a consultant for the FDA's Center for Devices and Radiological Health.

Samir S. Taneja, MD, is a consulting editor for the *Urologic Clinics of North America* and is on the editorial board of *European Urology*. He was recently inducted into the American Association of Genitourinary Surgeons.

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ANNOUNCING

Tuition-Free Initiative Addresses High Student Debt

NYU School of Medicine announced in August 2018 that it will begin offering full-tuition scholarships to all current and future students in its MD degree program regardless of need or merit—a bold effort to simultaneously address the rising costs of medical education and still attract the best and brightest students to careers in medicine. "This decision recognizes a moral imperative that must be addressed, as institutions place an increasing debt burden on young people who aspire to become physicians," says Robert I. Grossman, MD, the Saul J. Farber Dean of NYU School of Medicine and CEO of NYU Langone Health.

(Photo credit: Juliana Thomas Photography)

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