National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
2007 NIDDK Prostate Basic and Clinical Science
Strategic Planning Meeting

July 17–18, 2007
BWI Marriott
Baltimore, Maryland

Welcoming Remarks and Charge for the Meeting

On Tuesday, July 17, 2007, Steve Kaplan, M.D., Weill Medical College, Cornell University, opened the meeting and welcomed meeting participants. Dr. Kaplan told participants that this meeting will serve as a template for benign prostate research over the decade. Participants from four different areas of research will have the opportunity to collaborate on the future directions of research in this disease. The goal of this strategic planning meeting is to produce a document of research priorities and recommendations for future directions in basic and clinical research in benign prostate disease.

Following Dr. Kaplan's remarks, Rob Star, M.D., Acting Director, Division of Kidney, Urologic, and Hematologic Diseases (KUH), NIDDK, presented information related to the impact of benign prostatic disease. This presentation focused on the cost of benign urologic diseases per year, prevalence of benign urologic disorders (which are considered common), relative impact of urologic diseases as compared to other conditions (E.g., bothersome, large impact) for men and women and the quality of life, and the public health burden of this disease. Dr. Star tasked the group to provide NIDDK focal points with the relevant fields and directions. Dr. Star also described a new BPH/LUTS prevention initiative; prevention is another important area of concern, and emerging data suggests risk factors contribute to disease development.

Drs. Chris Mullins, Ph.D., and Lee Nyberg, M.D., Ph.D., of KUH, echoed similar comments on need to rejuvenate benign prostate disease research. Dr. Mullins stated that after this meeting, the Institute hopes to have the backbone for planning future research in this area. Dr. Nyberg emphasized that strategic planning meetings become the basis for how the Institute forms plans and workshops over the next decade and blueprints future research plans.

Basic and Clinical Research in Benign Prostate Disease: Challenges and Critical Need for Focused Efforts

Dr. Mullins presented information about NIDDK support of benign prostate research and provided details related to the funding and scientific trends associated with benign prostate diseases: During the presentation, Dr. Mullins noted that funding for the National Institutes of Health (NIH) doubled from 1998 to 2003, and focused on research efforts for benign prostate research since the Fiscal Year doubling. After the Fiscal Year funding increase, NIDDK has awarded fewer new and renewal grants. In fact, statistics

show a dramatically larger decrease in benign prostate research since 2003, than was seen for in overall NIDDK research in this same period. In addition to this issue, a significant drop in the number of new principal investigators (PI) focused on these diseases has occurred. Dr. Mullins concluded by asking participants to ponder the following questions during this meeting: What should be the research priorities and future directions driving the NIDDK and the benign prostate research community? How can we revitalize this research area? What should be the community's research focus at the NIDDK?

Dr. Star's presentation on advancing urologic science and career development discussed problems in urology research related to attracting new and retaining established benign prostate researchers in this field. During his presentation, Dr. Star noted that urology applications are not always as competitive as applications from other fields. His discussion also focused on special quality of life issues, uro-centric issues, and how to advance urology. This presentation also highlighted KUH actions for FY 2008. In addition, Dr. Star discussed proposals and actions from the American Urological Association.

John Wei, M.D., University of Michigan, presented information on the economic impact of benign prostate disease. Dr. Wei noted the following statistics related to the economic importance of this disease:

- Benign prostate hyperplasia (BPH) ranks fourth in urologic diagnoses in annual medicare expenditures;
- One in three patients see a doctor for BPH or lower urinary tract syndromes (LUTS), as opposed to prostatitis.
- BPH is common among older populations, and prostatitis is more common among younger populations.

Other topics of Dr. Wei's presentation included:

- Differences between BPH and prostatitis
- Trends in utilizations of pharmacologic agents for BPH and prostatitis
- Estimates drug therapy costs
- Trends in surgical procedures of BPH
- Rates of surgery/procedures for prostatitis

Dr. Wei also noted that annual individual expenditures for BPH averaged $1,536, and for prostatitis, averaged $1,759. Another important point in this presentation included a discussion of indirect costs associated with these conditions. Indirect costs include lost productivity, which contributes to overall costs. Lastly, Dr. Wei informed participants that the National Economic Burden direct costs for prostatitis was $1.8 million and BPH $7.7 million, excluding medication costs.

Process and Strategy for Development of a Prostate Strategic Plan

Dr. Kaplan spoke to meeting participants about how to advance this field of research. As the population ages, there will be a growing need to advance research in this area. Dr. Kaplan asked participants to focus on concepts rather than terms and to think of this area

of research as multidisciplinary, not separate from other health issues. For example, how does obesity affects urology diseases? He described how this field can merge with others, and therefore, increase research initiatives and efforts and create additional opportunities for benign prostate research. Dr. Kaplan's discussion also included:

- How to overcome potential barriers to performing benign urologic research. He noted that researchers are dealing with disease entity without fully understanding the basic mechanisms of this disease.
- How this community can affect change as well as priorities and tools that researchers can use. Dr. Kaplan stated that this community will affect change by: Focusing on science rather than quantity of funding and setting up scientific templates to affect change.
- How to implement the prostate research strategic plan. During this discussion, he pointed out the four planning committees: basic science, epidemiology/population based studies, translational opportunities, and clinical sciences.
- The timeline for developing the prostate strategic plan. In January 2006, NIDDK received concept clearance approval. The Institute plans to present and distribute this document by Winter 2008.

Scientific Focus Group Visions

The four breakout groups provided a brief presentation of the topics their group wished to discuss. Topics from each group are listed below:

Basic Science:
(Co-Chairs: Drs. Natasha Kyprianou and Wade Bushman)

- Prostate stem cells
- Animal and cellular models—Lessons learned from in vitro models
- Cell-cell interactions—Stroma-epithelial interactions, tissue microenvironment
- Vasculature—Angiogenic responses of normal & benign prostate, Anoikis regulation, endothelial cell component dictating prostate epithelial cell responses
- Hormonal action—The role of androgens and estrogens; generation of AR and ER knockout mice and their availability as molecular tools to dissect hormonally-regulated signaling/interactions in the prostate
- Signaling cascades—Cell Proliferation, Apoptosis, Vascularity,
- Inflammation
- Embryology—Signaling pathways operating in prostate embryonic development, embryonic awakening morphological patterns,
- Aging—Effect of declining androgens, epigenetic changes, DNA methylation, inflammation
- Metabolism—Significance of zinc transporters, citrate in prostate growth
- Neuronal influences Growth factor signaling, axonsl-cell interactions
- Genetics/genomics—Functional genomics, characterization of new molecules regulating prostate apoptosis and cell cycle progression/arrest
- Proteomics

- New technologies and methodologies (e.g. miRNA approaches, nanoparticles)

Dr. Bushman added that most professionals in the urologic research field are interested in cancer research and that there is a lack of interest in prostate biology. He commented on the need to foster learning for new prostate biologists, and he also noted that BPH is a prostate/bladder disease. Prostate biologists should maintain collaborations with bladder professionals.

Epidemiology/Population-Based Studies:
(Co-chairs: Drs. Quentin Clemens and John Wei)

- Epidemiology of Prostatitis—methodologies, incidence, prevalence, and natural history
- Epidemiology of Prostatitis—risk factors/comorbidity, prognostic factors, sequelae, association between prostatitis and prostate cancer
- Epidemiology of BPH—mechanisms of BPH/ED association, OAB vs BOO, reversible risk factors such as obesity, smoking and metabolic syndrome
- Diffusion of technologies, therapies incl. medications and supplements
- Practice Patterns for BPH—use of resources, follow-up care, PCP vs Urology, health education
- Practice Patterns for Prostatitis—use of resources, follow-up care, primary care physician vs urologist health education
- Quality of Care for BPH and Prostatitis—Overuse, underuse, timeliness of dx, development of quality indicators
- Quality of Life—measures and implementation into clinical practice
- Costs
- Decision making for BPH

Drs. Clemens and Wei also noted that additional topics their group will discuss include:

- The role of population-based science in prostate disease
- BPH versus prostatitis
- Risk factors, comorbidity, unmet needs, changing paradigms, epidemiology observations, quality of care (what defines quality of care)
- Quality of care and cost analysis
- The challenge of merging epidemiological observations into clinical trials

Translational Opportunities:
(Co-chairs: Drs. Robert Getzenberg and Scott Lucia)

- Biomarkers
- Genome scanning
- Genetic linkage (polymorphisms)
- Epigenetics
- Bioinformatics
- Pathologic changes associated with disease focusing on clinical trials
- Tissue, serum, urine resources
- Database studies

Dr. Getzenberg commented regarding the difficulty of translating needs into the clinic and noted the lack of expertise in translational research. He stated that there is a need to recruit more professionals in this area. Dr. Lucia told meeting participants that translation is the movement of concepts from more basic science to the clinical setting, the utilization of technologies to better define and stratify clinical populations, and the development of resources that facilitate advancement of basic studies to the bedside.

Clinical Sciences:
(Chair: Dr. Claus Roehrborn)

- Definitions and their importance (BPH, BPE, BOO, LUTS)
- Types of trials: population based studies, cross sectional, longitudinal, registries prospective cohort studies, controlled trials
- Issues in clinical trial design: Methodologies, Disease metrics, Presentation and publication issues
- Goals of trials: Treatment of signs and symptoms, Prevention trials, Integrative Physiology, Omnibus studies
- Specific Study Concepts (hypothesis driven): Implications of PSA changes—anti-inflammatory, 5-alpha reductase inhibitors
- Specific Study Concepts (hypothesis driven): Complementary medicine, Inflammation and LUTS, LUTS and sexual function, Phytotherapeutics in LUTS/BPH and inflammation
- Specific Study Concepts (hypothesis driven): Metabolic syndrome—intervention, Aging, and LUTS
- Specific Study Concepts (hypothesis driven): Comparison of available MIST intervention, Comparison of surgical treatments (e.g. TURP vs various lasers etc)
- Technology Assessment Panel for LUTS/BPH treatments

Also, Dr. Roehrborn stated the goals of the clinical sciences group:

- Review the individual write ups
- Eliminate overlaps
- Avoid given equal weight to each topic and discuss most important information
- Produce integrated document which may serve as white paper of research needs in clinical sciences for BPH/LUTS

Scientific Focus Group Breakout Sessions: Identification and Prioritization of Needs and Directions for Research in Benign Prostate Disease

Immediately following Dr. Roehrborn's visions for the clinical sciences group, the four subgroups met individually to discuss the tasks of identifying, prioritizing, and assessing the needs for their group. Another important part of their task included assigning directions for research in this area. A comprehensive document containing each subgroup's prioritized areas of need and suggestions for future research directions is anticipated to be published in Winter 2008.

Scientific Focus Groups Present Prioritized Recommendations for Benign Prostate Disease Research for Group Comment

Following the breakout session meetings, the co-chairs from each group presented recommendations on several topics. It is important to note that a strategic planning publication including comprehensive information and recommendations is forthcoming and will provide extensive details regarding these recommendations. After each presentation, each subgroup requested feedback from the larger group.

Basic Science

Dr. Bushman presented recommendations from the basic sciences group. He noted many discrepancies exist between what basic scientists think about and what urologists hear (E.g., prostate stem cells versus prostate growth). He presented the following recommendations on behalf of the basic sciences group:

- Study growth regulation using an integrative approach (e.g., how do hormones relate to other physiological issues?).
- Study inflammation and aging using an integrative approach (e.g., prostate stem cells and senescenece).
- Solve the causes of lower urogenital dysfunction by focusing on bigger button issues like aging and metabolism.
- Use symptom analysis in animal models to measure sensory function in animals as it relates to pain in the prostate and bladder.
- Consider how difficult it may be to move what needs to be done into a mechanism that effectively targets efforts.
- Discussed the concept of developing a Gordon conference to bring people to a large venue and encourage cross-talk among professionals. Participants would leave with new ideas to take back to their labs.

Group members noted the following comments:

- What are the existing model systems and critical needs for improvement in those systems? Focus on transgenic models. Mouse models have not been studied as well as they could be; a lot more could be done with existing models.
- Another member echoed the critical need for mouse models. Need ways to look at stromal hyperplasia. Create a mouse model that obstructs and the kidney and bladder researchers will also be interested.
- How can the group integration clinicians? What do they need? What are they getting?
- Access to tissue is a need and tissue bank repositories are critical. Fresh tissue is needed to assist translational research efforts.
- Another need is to relate hormones and other things to a normal human prostate. Normal human prostates are needed to learn about interactions with other issues.
- There is a need to support the new generation of urological researchers through fellowships. Basic scientists are serving as mentors for fellows.

- A discussion about training programs ensued. Someone noted that training programs are needed for fellows. This encourages greater interaction between basic scientists and fellows. Basic scientists mentor urologists and clinical researchers have to mentor basic scientists. This should be bidirectional in terms of learning and nurturing new professionals into this field.

Epidemiology/Population-Based Sciences

Dr. Wei began his presentation to the group by discussing some challenges related to the epidemiology of prostatitis:

- No data exists for the epidemiology of prostatitis in minority groups
- A need to determine the natural history of Type III prostatitis
- ICD coding should be changed to correspond to the NIH prostatitis classification scheme
- Limited information about disease risk factors and prognostic factors (as it relates to the link with clinical data and biorepository such as tissue, blood, urine, etc.)
- How to cope with symptom fluctuations over time

Prioritized recommendations for the epidemiology/population-based studies of BPH:

- Clearly define phenotype of interest (OAB, BOO, LUTS)
- Establish risk factors for change in natural history
- Place emphasis on modifiable risk factors
- Study primary and secondary prevention (biomarkers)
- Study design must be appropriate for question
- Obtain better evidence for patient safety, decrease cost of other rationale for using new technology (diffusion of new technologies)
- Place emphasis on use of EVBM and outcome data
- Practice Patterns BPH/ Prostatitis
- Provide better education for primary care providers and urologists with regards to use of measures (CPSI, ISS0, outcomes and best practices (guideline). Patients "run the gamut" of treatment options and discuss difference between BPH and prostate cancer.

Group members noted the following comments:

- How do you integrate epidemiology/population-based with basic science? If a basic scientist discovers a biomarker that is measurable, the epidemiology group should have a collection of specimens to test the biomarker.
- Chemists and urologists working in population based studies should have the potential for real collaboration.
- Study requirements should be consistent with the specimens used in the study. More specimens need to be available for different types of research. Patient profiling and use of phenotypes is also a concern.

Translational Opportunities

Dr. Lucia presented some of the following priorities for the translational opportunities group:

- Foster new investigators and establishment of working basic scientist-clinician research relationships.
- Develop standardized clinically significant disease/syndrome definitions that can be characterized by measurable phenotypic features.
- Define commonalities that are shared between clinical syndromes
- Develop serum, semen and/or urine based biomarkers which can identify progressive BPH.
- Identify serum, semen and/or urine based biomarkers that can identify men at risk of developing symptomatic BPH.
- Establish biomarkers for distinguishing various etiologic mechanism of prostatitis
- Exploit biospecimens, especially for benign disease
- Collaborate with other institutions

Group members made the following comments:

- Rather than using databases, do more footwork and figure out the process. How can clinical observations inform the translational process? Some clinicians perceive themselves as tissue suppliers for the basic scientists. The two sides should merge so that basic scientists will know the history of the tissue as well as the potential of the tissue.
- Structural problems: The perception for clinicians as specimen providers can result in difficult working relationships. Clinicians may not want to work with other researchers because of obstacles such as setting up meeting times, and the lack of description provided when responding to emails.

Clinical Sciences

Dr. Roehrborn presented an extensive list of prioritized recommendations for the clinical sciences group. Due to the length of these detailed recommendations, this list has been omitted from this report. However, more information and fine points will be provided in the forthcoming strategic plan for benign prostate disease. Group members made the following comments:

- Regarding trials that focus on changing lifestyle: are there any piggybacking options such as adding a cardiovascular component to it? Dr. Roehrborn responded that his experience in piggybacking has usually been very disappointing and there are a lot of obstacles such as the IRB, etc.
- Large studies are not necessary to demonstrate that lifestyle changes can be significant.

- Sufficient clinical trial activity: What are the obstacles? There are enough trials, but not the right type of trials. Most ongoing BPH trials are not significant, and fail to answer important questions or hit the right targets.
- There is a need for more new effective drugs.
- Surgical procedures are done at a fairly steady rate.
- Prostatitis is not mentioned in this group's section.

Closing Remarks

Dr. Kaplan thanked group for participation. Dr. Kaplan asked co-chairs to consider writing a summary paragraph to merge all four subfields.

Summary of Day 1 Activities and Strategies and Goals for Day 2

On Wednesday, July 18, 2007, Dr. Kaplan reconvened the meeting and noted a schedule change. Dr. Kaplan noted that the four subgroups would assemble earlier to create more opportunities for discussion. Among the requests made to the group were: 1) Developing a statement from each silo for outside readers, 2) Write a position statement regarding the group's beliefs, 3) Think about how we can evolve relationship between basic and translational/clinical sciences and provide recommendations for this goal.

Dr. Mullins asked participants to focus on paradigm shifts and noted that these involve new approaches to disease. He also asked the group to focus on moving the work forward and integrating science ideas.

Scientific Focus Group Breakout Sessions Resume: Refining of Research Needs and Priorities

Following the opening remarks made by Drs. Kaplan and Mullins, the subgroups met to further detail prioritized recommendations and suggestions from their groups. A comprehensive document containing extensive information regarding each subgroup's recommendations and prioritized areas of need is expected to be published in Winter 2008.

Group Refined Recommendations for Benign Prostate Disease Research for Group Comment

<u>Basic Science</u>

Dr. Bushman presented the refined recommendations for this group. Group members commented that:

- The mission statement would include working with the clinical community
- Dr. Kaplan commented that the bullets need to be fleshed out in the high-priority recommendations section. Dr. Bushman responded that these recommendations will be fleshed out in the chapter topics.

Epidemiology/Population-Based Studies

Group members provided feedback to this group. However, this commentary follows in a "general" section due to the universal application of the remarks.

Translational Opportunities

Group members provided the following commentary:

- Dr. Kaplan commented that the figure (diagram) illustration might be a good way to introduce a chapter or the entire book. Figures illustrate the connections between translational science and basic and clinical sciences. This shows how the four groups work together to form a collaborative approach to this disease.
- Several participants voiced the need for additional, expanded, and other common biorespository resources.

Clinical Sciences

Dr. Roehrborn commented that this group is working on an integration statement and noted that references would give health professionals from other areas of expertise additional resources.

- Dr. Bushman suggested that the clinical section precede basic sciences section in the forthcoming strategic plan document. Several participants agreed.
- A participant suggested using the translational opportunities subgroup's illustration figure to precede this information.
- Other participants expressed concerns regarding the length of this section.

General commentary for all sub-groups

- Bold out major focuses in the chapter, so chapter highlights are prominent
- References are to be provided judiciously. Drs. Mullins and Kaplan will be edited on an as needed basis. The Executive Summary will not contain references.
- Use consistent terminology/language in the mission statement, objectives, and general references in each section. (E.g., Participants may use the term "benign diseases of the prostate and related syndromes" when making a general reference.
- Dr. Kaplan requested consensus from participants regarding common language/terminology for BPH and prostatitis. Participants are asked to consider using terms such as chronic pelvic pain syndrome and benign diseases of the prostate and related syndromes?
- Another participant noted the terms BPH and prostatitis is more widely recognized by more health professionals than other terms.
- Dr. Mullins requested the use of numerous illustrations/figures in each section and noted there would be different themes highlighted throughout the book. Figures can be published or not published, but nonpublished figures would be easier to publish without asking for the journal's permission.

Summary Comments and Next Steps for Prostate Strategic Planning

Dr. Kaplan thanked participants for numerous contributions and presented the timeline for the strategic planning document. Co-chairs are to receive write-ups from their group no later than August 1, 2007. The anticipated peer review document will available in September. DKUH plans to publish the document by Winter 2008.

Dr. Mullins noted that this timely effort correlates with a genuine need for building interest in benign prostate disease. Dr. Mullins also commented that the subgroups began their efforts independently in their own groups, but have now melted together and introduced more ideas for cohesion among the groups.

Dr. Nyberg thanked meeting participants for their contributions.

Dr. Star noted that Dr. Kaplan will present this information to KUH subcouncil, and thanked everyone for their efforts.