

## James D. Brooks: prostate cancer screening awaits optimization to reduce inappropriate treatment

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### Editor's note

Prostate cancer, defined by the abnormal growth of cells, is a widely variable disease. According to the statistics of Prostate Cancer Free Foundation, prostate cancer is other than skin cancer the most common malignancy diagnosed in men with up to 1.1 million newly diagnosed cases each year (1). In the early 1990s, the use of early detection tests for prostate cancer became prevalent in the United States. It indeed is helpful to detect a wide range of prostate cancers at an early stage, but there remain uncertainties of whether the benefits of screening outweigh the risks for most patients. Commonly used tests such as the prostate-specific antigen (PSA) test and digital rectal exam (DRE) often result in abnormal test results, either false-positive or false-negative, that lead to either overtreatment, inappropriate treatment or lack of treatment (2).

Whilst many doctors are struggling over whether certain patients need treatment or active surveillance (AS), an approach by which patients are monitored closely without undergoing treatment right away, Prof. James D. Brooks from the Department of Urology at Stanford University is approaching the question from a totally different perspective—to study the cancer at the genomic and proteomic level and seek to develop biomarkers that more accurately detect the location of tumors. This time, *Translational Andrology and Urology* is pleased to interview Prof. Brooks, who will share with us his current research in the molecular and cellular characterization of screen-detected prostate cancer, the latest advances and challenges in prostate cancer detection and prognostication, the reason why AS is not widely accepted among patients, and many interesting findings and stories in his research.

### Expert's introduction

James D. Brooks, MD (*Figure 1*), currently serves as the



**Figure 1** Prof. James D. Brooks.

Keith and Jan Hurlbut Professor in the Department of Urology at Stanford University. He is also the Chief of Urological Oncology, Vice-Chair of the Department of Urology, and Associate Dean of Faculty Affairs in the Stanford University School of Medicine.

Prof. Brooks is internationally recognized for his work in cancer genomics and cancer biomarker development. His group has used a wide range of “omics platforms and next-generation sequencing” to understand prostate cancer biology and identify candidate disease biomarkers. In addition to running his own laboratory, he has participated in several cancer research consortia including The Cancer Genome Atlas (TCGA), the Early Detection Research Network (EDRN) where he was Associate Chair of the Prostate Cancer Working Group, and the Molecular and Cellular Characterization Center Consortium for which he serves as Co-Chair. While his primary research focus has been in prostate cancer, his other work includes kidney, bladder and testis cancer, as well as several benign urological diseases including obstructive nephropathy, benign prostatic hyperplasia and androgen insensitivity syndrome. His clinical practice centers on the screening and management of prostate cancer.

## Interview questions

**TAU:** *You have been using genomic and proteomic approaches to study prostate cancer for most of your career. How did you become involved in this line of research?*

**Prof. Brooks:** I came to molecular biology quite late in my training since my first exposure to it was in my early 30s during my research year in my residency. I was immediately taken by the ability of molecular methods to answer discrete questions about the underlying biology of cancer behavior in ways that were directly relevant to patients. I was very fortunate to come to Stanford shortly after Pat Brown had invented cDNA microarrays and joined a diverse group of scientists and clinicians that had coalesced around Pat and David Botstein to literally invent genomic scale research methods. It was thrilling. The obvious clinical application of genomic research was in identifying candidate biomarkers that could be applied to the clinical questions that I encountered daily in my practice: (I) how can we improve the performance of screening methods to tackle the problems of false positives and false negatives seen with PSA testing? (II) which cancers need to be treated and which can be safely observed? These questions remain at the focus of my research today.

**TAU:** *Would you introduce us to a current NIH-funded research project that you are involved in, including its goals, scale, duration of funding, current status and future directions?*

**Prof. Brooks:** I am the Principal Investigator on a U01 grant funded for 5 years by the Divisions of Cancer Prevention and Cancer Biology: "Molecular and Cellular Characterization of Screen-Detected Prostate Cancer". This is a large grant involving investigators in the Departments of Urology, Radiology, Pathology, and Biomedical Data Sciences at Stanford. We are part of a consortium of eight institutions that work in prostate, breast, pancreatic and lung cancer and are focused on understanding molecular and microenvironmental changes that occur in early-stage cancers and their precursors. Our site is using next-generation sequencing technologies to look at gene expression changes and DNA structural alterations in early prostate cancers and precursor lesions such as prostatic intraepithelial neoplasia. Our goal is to understand the early evolution of aggressive prostate cancer

and to understand whether there are evolutionary pathways that could represent "dead ends" in low risk lesions. We speculate that there are discrete molecular phylogenies that will allow us to identify indolent and aggressive cancers. With Sharon Pitteri's group at Stanford, we are also exploring proteomic and glycoproteomic changes in these early lesions using Mass Spectrometry methods that provide unprecedented detail of the location and types of N-glycosylation that decorates proteins in the normal and malignant prostate. These differences could serve as the basis for new biomarker approaches. We are about half way through the funding period and have completed profiling on over 200 microdissected prostate tissue samples and are expecting to publish our first findings within the next year.

**TAU:** *There are in the field a multitude of researchers studying prostate cancer biomarkers. What are the key differences between yours and those of other centers?*

**Prof. Brooks:** We have recognized there are three critical features needed for biomarker development: discovery, appropriate patient samples for testing and validation and, implementation platforms. Our discovery work has been diverse, encompassing genomic, proteomic and metabolomic approaches that have been selected with the view of applying our findings to identification of diagnostic or prognostic biomarkers. We have worked hard to assemble clinically relevant samples for testing and for definitive validation of biomarkers. This infrastructure is difficult to support financially, but we were fortunate to be funded by the Canary Foundation to collaborate with the University of Washington and several other sites to build multi-institutional resources including a large tissue microarray (TMA) resource and the Prostate Active Surveillance Study (PASS), a registry trial in which men placed on AS have systematic follow-up and sample collection for biomarker studies. Both the TMA and PASS cohorts have been designed for definitive testing and validation of candidate biomarkers. We have also been involved in early phase development and testing of platforms for measuring biomarkers. At Stanford, we have worked with bioengineers to test multiplex platforms, like MagArray, to measure candidate biomarkers, and scientists in the Department of Radiology to develop and test molecular imaging approaches such as targeted microbubbles and photoacoustic imaging.

**TAU:** *You work closely with bioengineers, radiologists, statisticians, geneticists, chemists and biochemists in studying biomarkers, molecular imaging, and protein and nucleotide detection on biological samples. What role does each of these parties play in your research?*

**Prof. Brooks:** Scientific research is increasingly being performed by teams, and this is reflected in recent data showing that the number of authors per paper has gone up dramatically over the past 3 decades. For me, the most impactful and exciting projects have been collaborations with investigators that have diverse backgrounds and expertise in which we all contribute something unique to the project. This type of research can be tricky to execute and requires time to develop while all of the collaborators to learn a common language and seek a common purpose. This incubation time is great fun while we learn from each other, argue about ideas and approaches and come up with our final line of investigation. As a translational scientist, one important challenge is to recognize that a new method or technique from another field can be used to answer a question that was otherwise difficult or impossible to answer previously. I find it is fairly straight-forward to galvanize interest from investigators in other disciplines around an important clinical question, particularly since funding sources target significant and relevant questions.

**TAU:** *AS is regarded as the best option to manage prostate cancers because it can preserve the sexual function and the quality of life of patients, but recent studies have shown that this method is not as popularly chosen by patients as expected. What do you think is the reason behind? How can patients' acceptance be enhanced in your opinion?*

**Prof. Brooks:** I agree that AS is a good approach for many men with localized prostate cancer, but there is high level evidence that shows that men with intermediate and high-risk disease should receive definitive therapy. All men with low risk cancer should be offered AS initially to manage their prostate cancer, and I believe that many more men with intermediate risk disease (e.g., grade group 2 cancers) should be managed with AS as a first step. The reasons for poor acceptance of AS are many, and include pressure on the patient from their family, friends and physicians, including some urologists, who hear the word cancer and assume the worst. We need to better educate the public and physicians about the natural history of prostate cancer and the perils of over-treatment. Uncertainty and fear about the

behavior of low and intermediate risk prostate cancer while it is being observed on AS is a second contributor to over-treatment, and this is where better biomarkers can help. Commercial assays will possibly help, but none of them have been validated in AS patients, despite the fact they are marketed for that use. I also think we need to better understand patient-centered outcomes as they relate to treatment and AS. We are engaged in an exciting project using big data mining and natural language processing algorithms to extract patient-centered outcome data from electronic health records to understand the urinary and sexual function in patients with localized prostate cancer. Once we and others collect robust data on patient reported outcomes while on AS and with treatment (e.g., surgery, radiation therapy), we can create patient-tailored decision aids to help patients navigate the treatment options for early stage prostate cancer.

**TAU:** *What are the latest advances and challenges in prostate cancer detection and prognostication?*

**Prof. Brooks:** It is remarkable how difficult it is to measure features of a 1 cc prostate cancer by sampling blood or urine from a 70 kg patient—it is a problem of scale. Finding molecular changes that are unique to prostate cancer cells, particularly those associated with aggressiveness, has proved to be incredibly difficult, particularly since early prostate cancers have few mutations. DNA methylation and protein glycosylation changes show the most promise for diagnostic biomarkers. Prognostic biomarkers have proven particularly difficult since one is essentially trying to predict the future. Gene expression changes in biopsy samples have been shown to be the most robust, but it is difficult to outdo Gleason score. Liquid based biomarkers including circulating tumor DNA or urine exosomes are beginning to show a lot of promise. The biggest changes in localized prostate cancer management in the near future will come from prostate imaging. If the high costs of imaging can be addressed, PET/CT and PET/MRI could improve on or replace multiparametric MRI. As more tests come to the market, I am concerned most patients will receive most of these tests, and that the costs of treating localized prostate cancer are going to skyrocket without significant improvements in hard endpoints such as survival or quality of life. A very important area of clinical research over the next several years will be to determine which tests provide unique information and which are redundant, and to determine the order in which the tests should be performed

to reduce the number of unnecessary biopsies, over-detection, over-treatment, costs and mortality.

**TAU:** *Over the years, you have led a number of clinical trials relating to prostate cancer management. Is there one that is particularly memorable to you? Why?*

**Prof. Brooks:** The projects funded by the Canary Foundation, mentioned above, have been some of my favorites. This collaboration made up of a team of very smart urologists, pathologists and statisticians who have great interpersonal chemistry and share a common interest in improving the management of early stage prostate cancer. When we started, we thought that it would be easy to build the TMA resource for testing and validating prognostic biomarkers that we would later use to select patients for AS. The TMAs that we anticipated would take us 6 months to make required almost 4 years to complete. Yet the rigor and thoughtfulness of the design of this resource made the delay worthwhile, and we all learned a lot by going through this process. This resource is really unique in that it meets the highest regulatory standards for biomarker validation. It has been gratifying that both PASS and the TMA resource have generated important, practice-changing findings.

**TAU:** *As a professor in urology, what would be your advice to students who would like to be successful in your field?*

**Prof. Brooks:** Mentors are critical to a young person's development, and it is important the mentor be committed to the long-term success of the mentee. I was fortunate to have many great mentors and try to pass on some of their wisdom to my trainees. Some of my favorite advice includes: (I) pick an important question; (II) take the long view and avoid fights with your colleagues, especially over trivial issues like authorship; (III) as a trainee, you should almost always say "yes" when offered an opportunity you are interested in. However, do not over commit—you need to deliver on projects you have agreed to; (IV) as a junior faculty member, you need to learn how to artfully say "no"—especially requests to add a clinical or administrative task that does not advance your research

program. If you want to succeed as a translational scientist, your laboratory must be your top priority; (V) recognize that science has become a team effort, and work to be a good teammate; (VI) if you are a clinician, leverage your clinical expertise—you know what questions are important to you and your patients and where the pain points are in your practice; (VII) realize that luck, both good and bad, plays a role in discovery. During bad times, persevere; during good times, be humble; (VIII) early in your career, participate in grant review panels—it will give you an opportunity to see what successful grants look like and hone your skills in recognizing pitfalls in your own proposals; (IX) anyone interested in translational research should understand the methods of analyzing big data; (X) your work should be fun, exciting and interesting to you. If it isn't, you should be doing something else.

### Acknowledgements

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### Footnote

*Conflicts of Interest:* The author has no conflicts of interest to declare.

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