Collaborating to Move Research Forward: Proceedings of the 10th Annual Bladder Cancer Think Tank

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Meeting Report

Collaborating to Move Research Forward: Proceedings of the 10th Annual Bladder Cancer Think Tank

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Abstract. The 10th Annual Bladder Cancer Think Tank was hosted by the Bladder Cancer Advocacy Network and brought together a multidisciplinary group of clinicians, researchers, representatives and Industry to advance bladder cancer research efforts. Think Tank expert panels, group discussions, and networking opportunities helped generate ideas and strengthen collaborations between researchers and physicians across disciplines and between institutions. Interactive panel discussions addressed a variety of timely issues: 1) data sharing, privacy and social media; 2) improving patient navigation through therapy; 3) promising developments in immunotherapy; 4) and moving bladder cancer research from bench to bedside. Lastly, early career researchers presented their bladder cancer studies and had opportunities to network with leading experts.

Keywords: Bladder cancer, diagnosis, treatment, multidisciplinary

INTRODUCTION

The Bladder Cancer Advocacy Network (BCAN) is a non-profit organization whose mission is to increase public awareness about bladder cancer; to advance bladder cancer research; and to provide educational and support services for the bladder cancer community. Since 2008, BCAN has sponsored the annual Think Tank, which has served as a vehicle for advancing clinical and research understanding of the underpinnings of bladder carcinogenesis. This report summarizes the 10th Bladder Cancer Think Tank and provides a review of the working groups as depicted in Table 1.

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Table 1
Key points

1. Data sharing, privacy issues and social media influence how research is disseminated and researchers should use caution in using and interpreting findings from 'large data'.
2. Analysis of patient experience and research regarding enhanced recovery after surgery (ERAS) program in bladder cancer is promising with further refinements balancing risks versus benefits implementing such protocols.
3. The use of xenografts and other bench to bedside have expanded how bladder cancer modeling can be used to advance the field and lead to potential for improvements in patient care.
4. The role of alterations within the DNA repair gene ERCC2 as a predictor of response to cisplatin sensitivity can be used to prospectively select those bladder cancer patients who are most likely to respond to cisplatin-based chemotherapy.
5. The first trial exploring immune checkpoint blockade in bladder cancer involving the administration of two doses of the CTLA-4 inhibitor, ipilimumab, prior to cystectomy in patients with invasive bladder cancer which shows promise for future trials including recent phase I studies of pembrolizumab and atezolizumab.
6. The increasing importance of radiation therapy as an immunomodulatory treatment modality provides a basis for combinatorial approaches involving radiation and immune checkpoint blockade which may be an "abscopal" effect

COLLABORATING TO MOVE RESEARCH FORWARD

The meeting, chaired by Dr. Ashish M. Kamat from MD Anderson Cancer Center, Houston and Dr. Jonathan Rosenberg from Memorial Sloan Kettering Cancer Center, New York, attracted over 200 attendees representing nearly 80 medical institutions and five countries. Dr. James Doroshow, Director of Division of Cancer Treatment and Diagnosis, Deputy Director for Clinical and Translational Research at the National Cancer Institute, delivered the keynote address on reducing the timeline for developing cancer drugs.

Developing new molecularly targeted drugs for patients with cancer presents unique challenges for clinical drug development research. Increasing complexities of drug discovery and development, lack of validated preclinical disease models for predicting human efficacy, prolonged timelines for clinical evaluation, and high failure rates have highlighted the inadequacies of the current clinical development paradigm.

At present, approximately 75% to 95% of agents entering Phase I clinical trials for oncology indications fail to achieve FDA approval; the majority of these failures occur late in clinical development, adding to the cost and time to develop effective new therapies. Estimates for the cost to develop a drug in the United States are approximately $2000 million, with the most money being spent later in the development. A further consideration is that the current clinical trial process, with traditional endpoints, could result in hundreds of patients being treated with ineffective therapies. This is an inherent risk of clinical trials, however, this presents an issue only if it diverts patients from effective therapies. Approximately 30% of agents fail due to lack of efficacy, and this often occurs late in development.

One approach to improving the timeliness of cancer drug development is to focus on producing "clinically ready", qualified assays to assess engagement of the drug target under study early in preclinical testing; these assays can then be applied during first-in-human clinical trials. Definitive correlation of drug efficacy with inhibition of the agent's presumed target, as well as correlation of tumor target inhibition with that in normal tissue surrogates, should be developed from *in vivo* studies in preclinical model systems utilizing procedures that can be transferred directly to the clinic. This approach could significantly improve the level of information developed from first-in-human studies; and although such a model shifts resource utilization and costs earlier in the development process, it allows for the evaluation of molecular proof-of-mechanism during the initial clinical trials of the drug and the ability to correlate target effects in pre-clinical systems and patients simultaneously ultimately leading to decreased costs. The availability of molecular target validation assays that have been employed in the clinic during phase I trials also permits more definitive assessment of target inhibition in tumor and surrogate tissues during phase II studies, potentially shortening the drug development life cycle.

SESSION 1: DATA SHARING, PRIVACY ISSUES, AND SOCIAL MEDIA

Co-chairs: Wassim Kassouf and Trinity J. Bivalacqua

A portion of the session and small group discussion focused on the role of social media in bladder cancer. David Cooke, program director and head of thoracic surgery section at UC Davis presented his experience with social media in lung cancer. This was of particular interest as the lung cancer patient population share similarities with the bladder cancer patient population with respect to patient

socio-demographics, risk factors. He pointed out the various roles of social media in medicine and urology. It can act as an instant press release for rapid dissemination of information. It can serve as an avenue for live broadcasts. From a patient perspective, social media have the potential to increase patient engagement as they go through their journey with the disease and harness support groups that will potentially lead to improving quality of care for patients. One can develop a disease specific social media community, which among other goals, can provide input into patient-oriented research. For example, PCORI (Patient-Centered Research Outcomes Institute) have utilized social media platform and public medical communication to develop two-way learning to (a) introduce strategies for evidence-based decision making for patients and families, (b) disseminate evidence-based information on the treatment of lung cancer & the results of comparative effectiveness research. Cautionary examples were highlighted to ensure HIPAA regulation is always respected and control of content guided by the institutional social media guidelines.

Our second speaker, Dr. David Miller who is a urologist at the University of Michigan shared his experience using the Michigan Urological Surgery Improvement Collaborative (MUSIC). The overall aims of the collaborative include evaluating and improving patterns of care for prostate cancer. Examples of current initiatives include radiographic staging of men with newly diagnosed prostate cancer, reducing biopsy-related complications and assessing repeat biopsy patterns, improving patient outcomes after radical prostatectomy, enhancing patient-centered decision making among men considering local therapy for early-stage prostate cancer, and understanding and reducing variation in the use of androgen deprivation therapy. Participating practices submit data to a clinical registry maintained by the MUSIC Coordinating Center and review risk-adjusted measures of processes of care and patient outcomes, and identify strategies and best practices for quality improvement in the way cancer care is provided to patients. MUSIC is managed by the MUSIC Coordinating Center, which is housed at the University of Michigan. Support for MUSIC is provided by Blue Cross and Blue Shield of Michigan. Dr. Miller demonstrated that state wide investment in education of all prostate cancer practitioners mostly urologist in a single state can result in the improvement in cancer care and process of delivery to prostate cancer. This resulted in a decrease in overall complications from surgery, prostate biopsy, and misuse of axial imaging in low risk prostate cancer. Using the MUSIC platform, his group has shown that education of urologists about the utility and efficacy of perioperative mitomycin C following transurethral resection of bladder tumor (TURBT) can improve the process of care to non-muscle invasive bladder cancer patients in Michigan [1]. Other areas in bladder cancer where the MUSIC platform would be appropriate include the use of intravesical therapies including BCG + maintenance therapy and chemotherapy in patients who fail induction BCG, appropriate candidates for neoadjuvant chemotherapy, and use of trimodality chemoradiation and surgery for muscle invasive bladder cancer. As our healthcare insurance companies move to cost effective evidence based therapies, using collaborative efforts to deliver the best quality cancer care for all patients is forthcoming. Bladder cancer specialists need to organize such collaborative efforts to be ahead of the curve in this area of research.

Our last speaker, Dr. Keith Baggerly from MD Anderson Cancer Center, is a bioinformatics statistician who shared with us some lessons learned from analyzing large genomic data sets. It is common in the literature for scientists to treat cancer cell lines or pre-clinical cancer models with therapeutic agents (chemotherapy, immunology, target therapies, etc.) and evaluate gene expression changes to determine the mechanism of action of selective therapeutics. These data are then used to initiate clinical trials for the treatment of localized and advanced cancers. However, Dr. Baggerly pointed out that as physicians and scientists, we must perform a number of simple tests to confirm the large data published in the scientific literature. When large genomic data are published online, the information is public for everyone to utilize and also to confirm the findings. He shared his experience using "omic-based signatures" as biomarkers of disease pathobiology, stressing the need to verify that the data has been assembled correctly. The use of "forensic bioinformatics" is sometimes performed to confirm the data which is available in the published literature. Examples of mistakes that can occur when big data is analyzed include confounders in the experimental design such as sample, genes, and treatment groups that are mislabeled and thus final data analysis can be incorrect. These mistakes can influence patient care. In the US alone, approximately $60 billion is spent annually on preclinical research, much of which cannot be reproduced by external investigators! The causes of these

irreproducible results include study design, laboratory protocols, data analysis/reporting, and biologic reagents mishandling. In summary, critical thinking in evaluating big data is necessary, and all experiments are subject to validation and critical appraisal. Without confirming results prior to initiating clinical trials in cancer patients, we are potentially subjecting our patients to unnecessary treatments with no biologic evidence of effect.

SESSION TWO: PATIENT NAVIGATION PANEL

Co-Chairs: Sia Daneshmand and Jay Shah

This panel focused on the management of bladder cancer with emphasis on the patient experience. We started out the session by hearing from three patients and their path to treatment. One of the unique aspects of this meeting is the ability to incorporate patients' perspectives and experience into the scientific program. Dr. William Shipley emphasized the importance of bringing in the voice of the patient and that integrated decision-making can facilitate education as well as trial recruitment. He pointed out that bladder preservation protocols using chemoradiation are approved for selective use by various guidelines committees, are well tolerated, and are associated with high cancer specific survival rates. Patients should be made aware of these protocols and can be directed to team based or multi-disciplinary clinics

Dr. Donna Berry discussed issues surrounding incorporation of patient preference in decision-making. Bladder cancer management relies heavily on patients' choices regarding the type of treatment as well as preference regarding urinary diversion. There is a highly complex interplay between the providers' presentation of data as well as patient factors and characteristics that can influence the decision process and outcomes. There is currently no evidence-based system to facilitate the decision process. Dr. Berry presented results of an exploratory study using Grounded Theory methods of data generation and analysis, with 60 participants recruited and interviewed from a multi-disciplinary genitourinary oncology clinic and two urology clinics in Boston. Patients were asked about their decision-making process including information sources, worries, the influence of work or family roles and how much the participant felt they 'shared' in the decision making. There were some poignant quotes presented from the patients. The results showed that men began their decision-making with the site of care (60% vs 33%) and recommendation of the cancer center physician (62% vs. 47%) more often than women. The only influential factor that women voiced more often than men (53% vs 36%) was expected recurrence/survival rates. This is helpful data as we continue to refine our presentation of treatment options to patients and look forward to additional data from this ongoing study.

Intimately related to the concept of patient navigation is enhanced recovery. Dr. Jay Shah described the optimized surgical journey (OSJ), which is an enhanced recovery after surgery (ERAS) program. He presented data on bladder cancer specific symptom index to better understand the patient experience, so we help navigate them through the highly stressful perioperative period. Improvements in surgical technique, anesthesia, and pathway driven post-operative care, have resulted in reduced morbidity and length of hospital stay. The mean hospital stay however at most centers remains high at 10-11 days [2]. ERAS protocols are evidence-based multimodal care pathways that aim to improve perioperative parameters for patients undergoing complex surgeries such as radical cystectomy. The goals are multi-factorial and include minimizing perioperative stress, improving short-term recovery and decreasing gastrointestinal complications which is the main cause of prolonged hospital stay [3]. Key factors in the ERAS protocol include preoperative carbohydrate loading, omission of bowel preparation and nasogastric tubes, focus on non-narcotic pain management, early feeding and importantly the use of a peripheral mu receptor, alvimopan. Daneshmand et al. recently reported a dramatic decrease in the hospital length of stay in 110 consecutive patients who underwent open radical cystectomy and urinary diversion (68% continent diversion) compared to matched controls. The median length of stay was 4 days compared to 8 days in the matched control with no increase in the readmission rates [4]. Most ERAS protocols, however, lack focus on patient-centered outcomes and do not measure patient symptom burden. Dr. Shah's preliminary data shows that the OSJ pathway leads to less abdominal discomfort, pain, difficulty walking and impairment of general activity, mood disturbance and relationship impairment and more enjoyment of life. However it was no better than traditional care pathways in decreasing fatigue, dry mouth and sleep disturbances associated with the surgery. Symptom burden will most likely directly correlate with poor recovery and measurement tools may allow

identification of under recognized factors and provide opportunities to address them.

Dr. Scott Gilbert led a discussion on measuring success in bladder cancer treatment. We commonly measure success with statistics regarding cancer specific and overall survival, complications rates, readmissions and functional outcomes. The goal of the lecture was to provide an alternative perspective to clinician-based outcomes and provide more patient-centered information that may be more reflective of the health status of the patient. This information may be adapted as clinical tools or questions that can help guide subsequent care. He pointed out data linking baseline quality of life deficits to poorer outcomes and lower survival rates in lung, colon and pancreatic cancers. There is additionally a randomized clinical trial in lung cancer demonstrating symptom reporting with notification to the clinical care team results in a lower symptom threshold event (19% vs. 8%) and better symptom control [5].

We concluded the session with presentations by Drs. Daneshmand (early cystectomy) and Kamat (BCG) focused on the difficult decision making process on management of high-grade T1 (HGT1) urothelial carcinoma. A recent meta-analysis of 73 studies including 15,215 patients with HGT1 tumors showed a 5-year recurrence, progression, and cancer-specific survival rates of 42%, 21%, and 87% [6]. Individual patient data were available for 2451 patients with a median follow-up of 5.2 years showing a 19% rate of progression and 91% disease specific survival with 79% of the patients not 'needing' a radical cystectomy. As expected patients not receiving BCG had a 78% higher chance of progression. There is universal agreement that variant histology is associated with significantly higher progression rates and that lymphovascular invasion (LVI) is considerably associated with a lower 5 years disease specific survival [7]. Dr. Daneshmand pointed out the fact that bladder cancer arises from a field cancerization effect and that HGT1 disease is potentially lethal with up to 30% progression and death rate with long-term follow-up. In one study, 8% of patients with clinical non-muscle invasive bladder cancer had positive lymph nodes, though this was mostly in the era prior to the recommendation for repeat TURBT [8]. There are data to suggest that BCG delays recurrence but may not impact cancer specific survival and that delaying cystectomy for initial high-grade T1 disease leads to a significant decline in cancer specific survival [9, 10]. Advantages of early cystectomy would be obtaining accurate pathologic staging, higher chance of being able to perform nerve-sparing approaches, avoiding multiple intravesical treatments and better cure rates. It is clear that as clinicians we need to amalgamate the patient perspective as well as clinical information to optimize bladder cancer treatment.

SESSION THREE: TRANSLATIONAL SCIENCE IN BLADDER CANCER: FROM BENCH TO BEDSIDE

Co-Chairs: Gopa Iyer and John Taylor

In 2012, the efforts of the Translational Science Working Group were published reflecting expert consensus and experience with currently available pre-clinical models of bladder cancer [11]. The 2015 BCAN Think Tank convened a panel of experts to expand on this foundation by providing specific examples of how bladder cancer modeling can be used to advance the field and lead to potential for improvements in patient care. The panel provided successful examples of models used and their potential for, or already successful, impact on bladder cancer; moving from the basic science through clinical realms.

Dr. DeGraff discussed "Xenografting Techniques for Bladder Cancer Research" with a focus on tissue recombination. The experimental technique was reviewed and compared/contrasted to other methods including subcutaneous and orthotopic models. Tissue recombination involves placement of a graft under the murine renal capsule with tumor growth and animal sacrifice anywhere from 3 weeks to 3 months. Tissue recombination has distinct advantages in that it is a relatively low cost, rapid, *in vivo* model which allows determination of the individual contribution of stroma and epithelium to disease. This technique was first described in the 1970 s [12] with first use in bladder cancer in 2009 [13]. Dr. DeGraff then described his use of the model to determine the impact of FOXA1 on tumor growth with knockdown resulting in significant reduction in tumor burden [14]. Finally, he reviewed the use of the model to explore the impact of stroma, cancer associated fibroblasts, on tumor growth showing that there is a distinct impact on tumorigenesis as compared to fibroblasts from normal tissue, suggesting direct stromal involvement in tumorigenesis.

Dr. Xue-Ru Wu discussed animal modeling of bladder cancer with a comprehensive review of genetically engineered mouse models (GEMMS). These

models have led to discoveries such as; RTK/RAS activation accounts for most low-grade NMIBC [15, 16], loss of p53 and/or Rb are insufficient to drive development of MIBC [13, 17], the many divergent drivers for MIBC and possibly divergent progenitor cells, the distinct hormonal influence with deficiency in urothelial AR leading to resistance of tumorigenesis [18] and urothelial specific ERα gene knockout results in an increase in the incidence of cancer [19], and that currently available GEMMS offer a unique toolbox for the exploration of bladder cancer. He concluded with identification of the present challenges and opportunities in use of GEMMS, including but not limited to the late-onset and incomplete penetrance of some models, overcoming the rate-limiting step to metastasis, issues with gender in intravesical delivery of treatment and the associated cost of these systems.

Dr. Raghavan provided an overview of the advantages and limitations of some of the currently available bladder cancer model systems. These include urothelial carcinoma cell lines, established from patient tumors, as well as patient-derived xenografts. Once established, these models can be screened for sensitivity or resistance to specific therapies and sequenced to identify potentially targetable alterations of interest. As such, they have the potential to directly impact the clinical decision process and provide insight into individualized patient care. A significant degree of heterogeneity exists among established cell lines or xenografts. A panel of patient-derived xenografts that successfully grew in nude mice displayed a wide variation in chromosome number, cell division rates, and morphologic and immuno-phenotypic characteristics. One reason for such variability lies in the inherent lineage heterogeneity within a common bladder stem cell. Additionally, sub-lines derived from a single parental urothelial carcinoma line exhibited a wide variety of response to the chemotherapeutic agents doxorubicin and vinblastine. Dr. Raghavan discussed an advantage of orthotopic xenografts in their ability to mimic the tumor microenvironment of human bladder cancer. He described a study in which high resolution MRI was used to measure tumor volumes longitudinally in mice treated with chemotherapy. These measurements were found to be similar to direct caliper measurements of the same tumors, suggesting that non-invasive MR imaging is an accurate proxy for following tumor growth over time and for predicting cytotoxic responses in orthotopic models [20]. Finally, some limitations of xenograft models were discussed, including the requirement for an immune deficient environment for growth and proliferation, limiting the ability to investigate the role of the immune system in controlling tumor progression.

Dr. Van Allen discussed the role of alterations within the DNA repair gene *ERCC2* as a predictor of response to cisplatin sensitivity. He described an extreme phenotype study published in *Cancer Discovery* in 2014 [21] in which whole exome sequencing was performed on TURBT and radical cystectomy specimens from patients with muscle-invasive bladder cancer who had received cisplatin-based neoadjuvant chemotherapy. Surgical pathology was pT0/pTis in 25 patients (responders) and muscle-invasive or greater in 25 patients (non-responders). ERCC2 somatic alterations were found exclusively within the responders (36% vs. 0%, $p < 0.001$, Fisher's exact test) and ERCC2 was the only gene altered at a significantly higher rate within the responder cohort using an enrichment analysis that surveyed 3,277 genes that contained possibly deleterious somatic alterations. The ERCC2 mutant tumors also harbored a significantly higher mutation burden than wild-type tumors, suggesting that the identified ERCC2 alterations are associated with a defect in DNA damage response [22, 23]. All ERCC2 alterations were nonsynonymous point mutations within or in proximity to conserved helicase domains within the protein. These ERCC2 mutants failed to reverse cisplatin sensitivity when overexpressed within ERCC2 deficient immortalized xeroderma pigmentosa cell lines and conferred broad genomic instability. External clinical validation of ERCC2 alterations as predictors of cisplatin sensitivity is currently ongoing through the sequencing of platinum-treated bladder tumor cohorts from multiple institutions. These efforts may also define a genomic signature incorporating multiple DNA damage response gene alterations that can be used to prospectively select those bladder cancer patients who are most likely to respond to cisplatin-based chemotherapy.

SESSION FOUR: IMMUNOTHERAPY

Co-Chairs: Piyush Agarwal, Jason Efstathiou and Matthew Galsky

Though therapeutic modulation of the host immune system to treat cancer has been pursued since the time of William Coley in the late 1800's [24], and among the most successful cancer immunotherapies developed to date is utilized for the treatment

of non-muscle-invasive bladder cancer (i.e., BCG) [25], bladder cancer immunotherapy has recently entered a Renaissance era. In just the past few years, the development of novel and clinically active immunotherapeutic strategies for advanced disease, namely immune checkpoint blockade, have fueled the resurgence in interest in drug development in bladder cancer across the spectrum of clinical disease states. The Immunotherapy Session built upon the excitement in the field and featured a panel of experts covering key topics in clinical and translational cancer immunotherapy.

The session began with an introduction to immunotherapy in bladder cancer by Dr. Jason Efstathiou. Dr. Efstathiou set the stage for the session by providing a brief history of cancer immunotherapy and highlighting key developments in the field ranging from the development of BCG for the treatment of non-muscle-invasive bladder cancer, to recent mechanistic insights regarding the mechanism of action of BCG, to key clinical trials combining immunotherapy and radiation therapy [26–29].

Dr. Betsy Plimack subsequently provided an overview of clinical results to date with immune checkpoint blockade in bladder cancer. The first trial exploring immune checkpoint blockade in bladder cancer was a 'window of opportunity' trial involving the administration of two doses of the CTLA-4 inhibitor, ipilimumab, prior to cystectomy in patients with invasive bladder cancer [29]. This study provided proof-of-concept for immune checkpoint blockade in bladder cancer by demonstrating a perivascular influx of T cells in the tumor microenvironment in the post-treatment cystectomy specimen. While there have been no trials to date exploring single agent ipilimumab in patients with metastatic bladder cancer, a phase 2 trial has recently demonstrated an increase in peripheral blood CD8+ T cells after addition of ipilimumab to standard gemcitabine plus cisplatin [30]. Several ongoing trials are exploring the combination of CTLA-4 plus PD-1 or PD-L1 blockade in bladder cancer.

Dr. Plimack went on to summarize the results of the expansion cohorts of the phase I trials of pembrolizumab and atezolizumab enrolling heavily pretreated patients with metastatic bladder cancer. The phase Ia trial of atezolizumab enrolled 92 patients; enrollment was initially restricted to patients with tumor specimens expressing PD-L1 and was later opened to patients regardless of PD-L1 expression [27]. The objective response rate was 34%, and 20/30 responding patients continued to respond at the time of the data cut-off. The phase Ia trial of pembrolizumab enrolled 33 patients with tumor specimens expressing PD-L1 (in tumor cells) and the objective response rate was 28%. Similar to the results with atezolizumab, the majority of objective responses were durable. Importantly, grade 3-4 adverse events occurred in 8–15% of patients enrolled in these studies, which compares quite favorably with the adverse event profile of cytotoxic chemotherapy in this setting. While both studies demonstrated a correlation between higher expression of PD-L1 expression in tumor specimens and objective response rates, these studies utilized different assays, cut-points, and cells of interest (i.e., tumor cells versus tumor infiltrating cells) for PD-L1 expression complicating interpretation and synthesis of the results. Furthermore, both studies demonstrated that a small subset of patients with tumor specimens lacking PD-L1 expression still responded to treatment. The favorable toxicity profile with PD-L1 or PD-1 blockade, coupled with the durability of responses observed thus far, has led to tremendous enthusiasm in the field and trials designed to seek regulatory approval for these agents in patients with advanced bladder cancer have already completed enrollment.

Dr. Lawrence Fong discussed translational studies seeking to refine the mechanistic basis for the antitumor activity of immunotherapy through integration of immune monitoring of human biospecimens. In a study of ipilimumab in patients with castration-resistant metastatic prostate cancer, peripheral blood flow cytometry was performed to determine whether changes in the T-cell phenotype in the peripheral blood correlated with clinical outcomes [31]. Importantly, ipilimumab treatment was shown to increase levels of circulating T-cells including CD4+ and PD-1+ CD8+ T-cells. However, these changes did not correlate with improved outcomes indicating that while ipilimumab induces general pharmacodynamic effects, such changes do not fully explain the antitumor activity observed in a subset of patients. Dr. Fong's group subsequently utilized T cell receptor sequencing technology to better understand the impact of ipilimumab on the circulating T cell repertoire [32]. These studies revealed that CTLA-4 blockade induces remodeling of the T-cell repertoire leading to greater T-cell diversity. Importantly, maintenance of pre-existing high frequency T clonotypes were associated with improved survival in ipilimumab-treated patients with metastatic prostate cancer. These studies shed light on the T-cell biology underlying responsiveness to ipilimumab and while

these studies were performed in patients with prostate cancer, such observations are also critical in informing ongoing clinical and translational investigations of ipilimumab in bladder cancer.

Finally, Dr. Charles Drake discussed the increasing importance of radiation therapy as an immunomodulatory treatment modality and discussed the mechanistic basis for combinatorial approaches involving radiation and immune checkpoint blockade. Perhaps the first observations potential linking radiation therapy with systemic immunomodulatory effects were related to the "abscopal" effect, a term used by Dr. Mole in the 1950's to describe the phenomenon that treatment of a localized tumor could lead to shrinkage of distant tumors [33]. While there has been controversy regarding the frequency and clinical relevance of this phenomenon over the years, recent observations in the era of modern immunotherapeutic approaches have led to a resurgence in interest in the immunomodulatory effects of radiation. For example, studies in low grade lymphoma have demonstrated that injection of toll-like receptor agonists into an involved lymph node, along with low dose radiation, can induce regression of lymphoma at distant sites [34]. Postow and colleagues reported a case of a patient treated with metastatic melanoma treated with ipilimumab who experienced stable disease followed by disease progression on treatment [35]. The patient subsequently received radiation to a solitary site which was followed by regression of multiple sites of distant metastatic disease. The tumor regression was accompanied by an increase in circulating CD4+Icos^{hi} T cells along with an increase in antibodies to NY-ESO1. These studies have fueled additional clinical studies combining radiation and immune checkpoint blockade though additional insights from model systems are necessary to guide optimal combinations, treatments, and schedules.

2013 YOUNG INVESTIGATOR AWARD RESEARCH REPORTS

BCAN launched its Young Investigator Awards in 2013 to support the development of outstanding research scientists and clinical cancer research investigators who have demonstrated a commitment to improving the understanding and treatment of bladder cancer. Each award is for $100,000, over a two-year period. Three awards were granted in 2013, and those investigators presented their final reports:

David DeGraff, Ph.D., Penn State University Hershey, "Transcriptional Control of Bladder Cancer Tumorigenesis"
Gopa Iyer, M.D., Memorial Sloan-Kettering Cancer Center, "Identifying Predictors of Response to mTOR-targeted Therapies in Bladder Cancer"
Debashis Sahoo, Ph.D., University of California San Diego, "High-resolution molecular analysis of CD47-mediated immune escape in bladder cancer"

JOHN QUALE TRAVELING FELLOWSHIP AWARDS

Started in 2009, the John Quale Travel Fellowship Program provides stipends to defray travel-related costs for early career investigators interested in bladder cancer research to attend the Think Tank Meeting. Four young investigators were awarded John Quale Travel Fellowships to present their research at the 2015 Think Tank Meeting:

Abdul Banday, Ph.D., National Cancer Institute
Max Kates, M.D., Johns Hopkins Medical Institutions
Randy Sweis, M.D., University of Chicago
Huyen Nguyen, Ph.D., The Ohio State University

COLLABORATIVE SMALL GROUP DISCUSSIONS

Think Tank attendees participated in small group discussions during the meeting on a variety of different topics. Three working groups continued their collaborative efforts that had begun at previous Think Tank meetings: Survivorship Working Group, Upper Tract Disease Working Group and the Patient-Centered Outcomes and Policy Working Group. Nine other small groups continued the discussion of panel presentations or explored specific issues in bladder cancer treatment, including variant histology in bladder cancer; optimizing intravesical immunotherapy; optimizing surgical outcomes; mechanisms of invasion and metastasis.

CONCLUSIONS

The 10th Annual Bladder Cancer Think Tank brought together a multidisciplinary group of clinicians, researchers, representatives and industry in an effort to advance bladder cancer research efforts. Think Tank expert panels, group discussions, and

networking opportunities helped generate ideas and strengthen collaborations between researchers and physicians across disciplines and between institutions.

CONFLICT OF INTEREST

The authors have no conflict of interest to report.

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APPENDIX

Special thanks to the 2015 Think Tank Steering Committee

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