Meeting Report

The 19th Annual Prostate Cancer Foundation Scientific Retreat

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Abstract

Prostate Cancer Foundation (PCF) convened its 19th Annual Scientific Retreat October 25–27, 2012, in Carlsbad, CA. Each year, this event brings together diverse researchers in a collaborative forum to present and discuss new and largely unpublished findings for prostate cancer diagnosis, prognosis, and treatment and defines the challenges to ending this disease as a threat to life and well-being. Several themes resonated at the multidisciplinary meeting, notably (i) the roles of field cancerization, tumor microenvironment, epithelial plasticity, signal transduction pathways in cancer progression, and disease resistance; (ii) intratumoral heterogeneity and consequences for precision medicine; (iii) resistance mechanisms to androgen axis inhibitors; and (iv) advances in molecular imaging and therapeutics for better detection and treatment.

Introduction

For the 19th consecutive year, the Prostate Cancer Foundation (PCF) convened a scientific conference to (i) facilitate discussions on major unmet scientific and clinical needs for patients with prostate cancer among leading cancer researchers from academic, industry, and government institutions; (ii) attract investigators and ideas from other fields to solve prostate cancer challenges; and (iii) share the latest advances in basic, translational, and clinical prostate cancer research. The PCF Scientific Retreat serves as a forum for global knowledge exchange, dissemination of new findings, and charting progress for new innovations in treatment research for advanced prostate cancer. The multidisciplinary 19th Annual PCF Scientific Retreat, convened during October 25–27, 2012, at Carlsbad, CA, featured 55 scientific presentations and panels, one workshop, and 91 poster presentations. The meeting Program Committee was composed of 22 leading, extramurally funded senior and PCF Young Investigators who represented research programs in basic, translational, and clinical research. The "scientific demographics" of the meeting can be defined as having presenters and data drawn from 18 different scientific disciplines (basic science, tumor immunology, medical oncology, nuclear medicine, endocrinology, pathology, physiology, computational biology, radiation oncology, public health and epidemiology, surgery, molecular biology, urology, plant biochemistry, molecular imaging, clinical trials, genetics, drug discovery, and development). About 49% of presenters were first-time attendees presenting first-in-field and largely unpublished data. In total, 433 participants from 14 countries, 107 academic institutions, 41 biopharmaceutical companies, and 10 medical research foundations attended. This report aims to provide an overview of the research presented at the meeting. We apologize to the presenters whose work is not covered here for lack of space. A comprehensive summary of the presentations and the meeting agenda is available at www.pcf.org/2012RetreatReport.

Tumor microenvironment

The cancer-associated stroma or the tumor microenvironment is now recognized to play an important role in cancer progression and treatment resistance. Peter Nelson (University of Washington, Seattle, WA) showed that prostate cancer treatment (such as chemotherapy, radiation, etc.) induces DNA damage in the normal tissues surrounding a tumor. This genotoxic stress induces stromal cells to express a diverse set of growth factors and cytokines (such as WNT16B and SPINK1). WNT16B, whose expression is elevated 16-fold after treatment, increases invasiveness into the surrounding malignant prostate epithelium, resulting in resistance to therapy, treatment failure, and disease progression. These factors produced by the tumor microenvironment in response to therapy may serve as excellent drug targets to avoid the emergence of resistance. Neil Bhowmick (Cedars-Sinai Medical Center, Los Angeles, CA) identified a heterogeneous loss of TGF-β signaling in the cancer-associated stromal compartment as a cause for the multifocal and polyclonal progression of prostate cancer. He showed that paracrine pro proliferative signaling factors (hepatocyte growth factor and WNT proteins), proinflammatory cytokines (CCL2), and proinvasion cytokines such as the protein SDF-1 not only mediate localized prostate cancer progression but also metastatic progression to the bone. Mikala Egeblad (Cold Spring Harbor Laboratory, New York, NY) presented real-time microscopic imaging studies for preclinical models of breast cancer, showing that...
the microenvironment mediates treatment resistance by regulating vascular permeability and the recruitment of inflammatory cells to the site of the tumor.

Cancer Interception

Richard Mithen (Institute for Food Research, Norwich, Norfolk, UK) presented data on cancer interception, that is, “to actively intercept cancer development before the full-blown advanced tumor presents in the clinic.” Dr. Mithen is studying prostate cancer intervention using sulfonaphazines in broccoli, an epigenetic reprogramming substance that has anticancer activity. He has initiated a series of clinical trials in active surveillance patients to study the effects of sulfonaphazines in delaying the emergence of advanced prostate cancer.

Intratumoral Heterogeneity

Charles Swanton’s (University College London, London, UK) studies on core biopsies obtained from multiple spatially separated primary renal carcinoma tumors and associated metastatic sites revealed that 63% to 69% of all mutations are not detectable across every tumor region. His results suggest that genominc analyses from a single tumor biopsy, the current practice for cancer diagnoses and monitoring, may not be reporting the full mutational burden of these widely heterogeneous tumors. These studies have implications for precision medicine. Dr. Swanton and his team are currently evaluating heterogeneity in prostate cancer.

Molecular Imaging

Jamey Weichert (University of Wisconsin, Madison, WI) presented studies on new “diapeutics,” radiolabeled phospholipid analogs that allow broad-spectrum prostate cancer detection and radiotherapy. Preclinical results show selective uptake by tumors mediated by lipid rafts that are overexpressed in many cancer cells. Imaging studies with these materials show tumor uptake within 9 to 12 hours of injection and background clearance in 24 hours. Compared with conventional imaging agents, diapeutics provide the advantage of longer retention times, allowing better disease detection as well as treatment. Diapeutics are being tested in phase I/II clinical trials as positron emission tomographic (PET) imaging agents for several cancers—lung, brain, prostate, breast, pancreatic, and head and neck. One of these compounds, CLR1501, allows the illumination of the margins of a tumor in real-time during cancer surgery using a handheld Fluobeam microscope. This holds potential in enabling more complete and perioperative removal of malignant tissue.

Jason Lewis (Memorial Sloan-Kettering Cancer Center, New York, NY) presented results on 2 promising biomarkers that can be monitored by immuno-PET imaging for prostate cancer diagnoses and measurement of response to therapy. $^{99}$Zr-1591, fully humanized monoclonal antibody to prostate-specific membrane antigen (PSMA), serves as readout of aberrant androgen receptor (AR) signaling activity, whereas $^{89}$Zr-transferrin, a PET radiotracer that binds the transferrin receptor, serves as readout of biomarker of Myc status in prostate tumors.

John Kurhanewicz (UCSF, San Francisco, CA) reported results of hyperpolarized $^{13}$C magnetic resonance spectroscopic imaging as a novel in vivo metabolic imaging technique to image lymph node and bone metastases; to simultaneously image tumor metabolism and microenvironment; and to study response to androgen deprivation therapy (ADT) and treatment resistance.

New Therapeutic and Diagnostic Approaches

Results on new therapeutics and diagnostics in the pipeline were presented:

1. **OGX-427** targets Hsp27 whose production is induced by cellular stresses such as chemotherapy, radiation, and hormone therapy. Martin Gleave (University of British Columbia, British Columbia, Canada) showed the interaction of Hsp27 with AR in prostate cancer models, resulting in the enhanced expression of AR-regulated genes. Randomized phase II evaluation of OGX-427 showed that 71% of patients were progression-free at 12 weeks compared with 48% in the control arm. About 47% of patients who received OGX-427 plus prednisone experienced more than 50% decline in prostate-specific antigen (PSA) versus 21% of patients on the prednisone arm. These results provide the first credentialing for Hsp27 in the treatment of castration-resistant prostate cancer (CRPC). A randomized phase II study of OGX-427 in combination with abiraterone acetate in CRPC is being planned.

2. **ARN-509** is a potent small-molecule AR antagonist that impairs AR nuclear translocation and binding to DNA, inhibits tumor growth, and promotes apoptosis. Preclinical studies have shown that ARN-509 binds AR with a 10-fold greater affinity than bicalutamide in a competitive binding study against $^{18}$F-FDHT and induces tumor regression in hormone-sensitive and treatment-resistant animal models. Richard Heyman (Aragon Pharmaceuticals) presented an interim analysis of a phase II study conducted with ARN-509 in three CRPC cohorts: nonmetastatic ($n = 46$), treatment-naïve ($n = 25$), and post-abiraterone ($n = 14$); the data showed that ARN-509 was well tolerated and resulted in significant PSA declines in all cohorts. Five of 8 patients (63% overall response rate) with measurable disease at baseline in the treatment-naïve metastatic CRPC cohort achieved a partial response according to Response Evaluation Criteria in Solid Tumors (RECIST).

3. **Urokinase plasminogen activator receptor (uPAR)** interacts with its ligand, uPA, and the uPA-uPAR complex plays crucial roles in cell adhesion, cell-cycle regulation, cell migration, angiogenesis, and tissue remodeling. Andrew Mazar (Northwestern University, Evanston, IL) presented the development of 2 novel agents targeting the uPA axis: (i) ATN-291, a monoclonal antibody that targets uPA and exhibits antitumor activity in xenograft models. Dr. Mazar has
formulated ATN-291 in novel stealth liposomes termed nanobins that deliver the antibody selectively to cancer cells overexpressing the cognate receptor uPAR. (ii) ATN-658, a first-in-class humanized monoclonal antibody to uPAR that modulates numerous mediators of cancer cell signaling pathways and inhibits growth of metastatic lesions in bone and viscera in model systems.

4. Marc Diamond (Washington University, St. Louis, MO) presented results for the activity of pyrvinium, an intestinal parasite inhibitor, and its derivative, tetrahydropyruvinium (THP). These compounds cause conformational changes in the AR, resulting in prostate atrophy in models. THP also activates CSK1α, which targets the protein β-catenin for degradation. β-Catenin is an established AR cofactor. This novel mechanism of action will be exploited as a new prostate cancer therapy.

5. Kent Kirschenbaum (New York University, New York, NY) and Michael Garabedian (New York University) presented results on the rational design, synthesis, and characterization of linear and cyclic multivalent estradiol conjugates or peptides that specifically target AR nuclear translocation and gene expression in treatment-resistant prostate cancer cells.

6. Amina Zoubidei (Vancouver Prostate Centre, Vancouver, Canada) reported that enzalutamide activates Her2, which activates mitogen-activated protein kinase (MAPK) and AKT signaling. Preclinical combination therapy with enzalutamide and lapatinib, an Her2 inhibitor, showed promising inhibition in animal models and delayed the onset of enzalutamide resistance. These studies provide proof-of-concept that AR cotargeting is a promising strategy to control therapy resistance.

7. Scott Dehm (University of Minnesota, Minneapolis, MN) reported that AR splice variants act as independent effectors of oncogenic signaling. These variants drive persistent and constitutive activation of a large subset of AR target genes to support proliferation in cell culture and might be a cause of enzalutamide resistance.

8. William Redmond (Providence Portland Medical Center, Portland, OR) presented preclinical results of combination immunotherapy with OX40 and CTLA-4 monoclonal antibodies. This combination therapy caused potent antitumor immunity in prostate cancer models and deserves clinical evaluation.

9. Haydn Kissick (Harvard University, Cambridge, MA) presented the preclinical development of a peptide vaccine targeting the protein ERG in prostate cancer. This ERG295 peptide vaccine was immunogenic in humanized mice models and activates immune cells in the blood of patients with prostate cancer.

10. Brian Olson (University of Wisconsin) presented phase I results of a DNA vaccine against prostatic acid phosphatase (PAP) in 22 biochemically recurrent patients with prostate cancer. Eight of 22 patients had long-term immune responses to PAP and presented a novel population of regulatory T cells (Treg), which were PAP-specific, CD8+CTLA-4+, and secrete immunosuppressing IL-35. The presence of these novel, PAP-specific Tregs can serve as a biomarker to identify patients likely to respond immunologically to vaccination.

11. Nora Navone (University of Texas, Houston, TX) showed the clinical benefits of targeting the FGF–FGFR (fibroblast growth factor receptor) signaling axis for the treatment of prostate cancer bone metastases. The tyrosine kinase inhibitor, AZD4547, showed potent FGFR1, 2, 3, and 4 signaling inhibition.

12. Peter Kuhn (Scripps Research Institute, La Jolla, CA) described the development of a "fluid biopsy" approach that identifies circulating tumor cells (CTC; without using traditional cell surface protein–based enrichment) in patient blood samples. This enrichment-free "High Definition-CTC" assay detects more than 5 HD-CTCs per mL of blood in 80% of patients with metastatic prostate cancer. Temporal CTC characterization of a patient with prostate cancer revealed the evolution of cancer cells during treatment, showing that ADT and abiraterone alter AR expression.

13. Leileata Russo (Exosome Diagnostics, Inc.) described a urine-based, diagnostic test using urinary exosomes to reliably determine the presence and nature of a prostate malignancy.

14. Josh Lang (University of Wisconsin) presented the microluidic VeriFAST (Vertical Immiscible Filtration Assisted by Surface Tension) platform for integrated molecular CTC analyses. This system allows cell sorting, capture, purification, live cell intracellular and extracellular staining, and proteomic and genonomic analyses. The VeriFAST plat-form holds diagnostic and prognostic potential for patients with prostate cancer.

mRNA Translation in Cancer

Antineoplastic targets related to mRNA translation in prostate cancer was a first-time topic for this event.

1. Eukaryotic translation initiation factor 4E (eIF4E) is dysregulated in several cancers. Nahum Sonenberg (McGill University, Montreal, QC, Canada), who discovered the eIF4E protein about 30 years ago and has since studied its complex mechanism of action in cancer, showed that phosphorylation of eIF4E by Mnk1 and Mnk2 (MAPK–interacting kinase 1 and 2) promotes migration and invasion in preclinical models of advanced prostate cancer. Mnk1 and Mnk2 represent new experimental targets for prostate cancer therapy.

2. Kevan Shokat (UCSF) described rational polypharmacology that uses a combination of synthetic medicinal chemistry, kinase profiling, and a Drosophila-based phenotypic screen to identify potent lead compounds with early defined toxicity, targeting an ideal spectrum of tumor-relevant kinases while avoiding “anti-targets” (off-target kinases).
Clinical Classification of Prostate Cancer

Christopher Logothetis (University of Texas) presented a clinical classification of prostate cancer based on the underlying biology of the disease presented by patients. He suggested that prostate cancer can be broadly divided into 4 categories as a function of disease progression: Dihydrotestosterone-dependent, endocrine, endocrine/paracrine, and autocrine. Biomarkers are ascribed to each category and Dr. Logothetis is using this system to tailor therapy to individual patients. Of great interest is the emergence of resistant clones that are amplified during progression to the autocrine, AR-independent anaplastic state arising in great part by treatment selection, representing the most lethal form of the disease.

The Good, Bad, and Ugly of Preclinical and Observational Research

The PCF Scientific Retreat featured 2 presentations that discussed the limitations of experimental and observational research. The main theme that emerged from this session was "we get what we incentivize."

C. Glenn Begley (TetraLogic) presented the results of a 10-year long experiment at Amgen where his team attempted to replicate the results of 53 research studies credentialing new oncology drug targets but was successful in replicating only 6, that is, results claimed in only 11% of 53 studies stood up to the original assertions.

S. Stanley Young (National Institute of Statistical Sciences, Research Triangle Park, NC) suggested that the current observational study paradigm is "no correction for multiple testing or multiple modeling and no sharing of data sets" that he termed "Voodoo Statistics" and "Trust Me Science." He presented evidence of a false discovery rate for observational studies of more than 90%. Dr. Young invoked the principles of Edwards Deming, the pioneer statistician credited with the Total Quality Management movement that lays down principles to improve design, service, and product quality by using statistical methods.

Dr. Young contrasted the control of an observational study with that of a production process and gave technical explanations for the high false discovery rate and Deming reasons for why it continues. Dr. Young suggests that that we need to stop blaming the workers, that is, researchers and epidemiologists who conduct and analyze observational studies as they are responding to current incentives, publications, and grants. Therefore, the managers, that is, funding agencies and journal editors, need to redesign the rewards system.

Drs. Begley and Young proposed recommendations to investigators, institutions, reviewers, editors, funding agencies, advocates, and the press, so that methods of scientific pursuit and incentives for publication change for patient benefit.

Conclusions and Future Perspectives

The latest advances presented at the 19th Annual PCF Scientific Retreat 2012 are highly encouraging for patients and provide clinicians new tools to manage this life-threatening disease. The meeting fostered collaborations between all the disciplines of prostate cancer research; addressed several critical unanswered questions delaying better treatments for advanced prostate cancer; promoted academic, government, and industry awareness of the burning topics discussed; and catalyzed collaborative, transdisciplinary research efforts that will accelerate the search for a cure.

Overall consensus was that future investigations of mechanisms of treatment resistance, of the role of field cancerization and tumor microenvironment, and determining intratumoral heterogeneity and its impact on precision medicine are important and warranted. The AR signaling axis remains a crucial driver of prostate cancer progression and treatment resistance, and newer ways of targeting this axis hold potential to end death and suffering from this disease. The last 2 years have seen great progress in the treatment of CRPCs. This meeting continues to showcase these developments, as well as set the tone for future advances towards decreasing prostate cancer morbidity and mortality, being the focal point where the field comes together annually.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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