The 19th Annual Prostate Cancer Foundation Scientific Retreat: Meeting Report

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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year, this event brings together diverse researchers in a collaborative forum to present and discuss new and largely unpublished findings for prostate cancer diagnosis, prognosis and treatment and defines the challenges to ending this disease as a threat to life and well-being.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 1) the roles of field cancerization, tumor microenvironment, epithelial plasticity, signal transduction pathways in cancer progression and disease resistance, 2) intratumoral heterogeneity and consequences for precision medicine, 3) resistance mechanisms to androgen axis inhibitors, 4) 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 1) facilitate discussions on major unmet scientific and clinical needs for prostate cancer patients among leading cancer researchers from academic, industry and government institutions; 2) attract investigators and ideas from other fields to solve prostate cancer challenges, and 3) 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). 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.¹

**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, USA) 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, USA) 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), pro-inflammatory
cytokines (CCL2) and pro-invasion 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, USA) presented real-time microscopic imaging studies
for preclinical models of breast cancer demonstrating 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, UK) presented data on cancer interception, i.e. ‘to
actively intercept cancer development before the full-blown advanced tumor presents in the
clinic’. Dr. Mithen is studying prostate cancer intervention using sulforaphanes in broccoli, an
epigenetic reprogramming substance that has anti-cancer activity. He has initiated a series of
clinical trials in active surveillance patients to study the effects of sulforaphanes in delaying the
emergence of advanced prostate cancer.

Intratumoral Heterogeneity

Charles Swanton’s (University College London, UK) studies on core biopsies obtained from
multiple spatially separated primary renal carcinoma tumors and associated metastatic sites
revealed that 63-69% of all mutations are not detectable across every tumor region. His results
suggest that genomic 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, USA) 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 which are overexpressed in many cancer cells. Imaging studies with these materials show tumor uptake within 9-12 hours of injection and background clearance in 24 hours. Compared to 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 PET imaging agents for several cancers- lung, brain, prostate, breast, pancreatic, head and neck. One of these compounds, CLR1501 allows illuminating 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, USA) presented results on two promising biomarkers that can be monitored by immuno-PET imaging for prostate cancer diagnoses and measurement of response to therapy. $^{89}$Zr-J591, fully humanized monoclonal antibody to PSMA serves as readout of aberrant androgen receptor (AR) signaling activity, while $^{89}$Zr-transferrin, a PET radiotracer that binds the transferrin receptor serves as readout of biomarker of Myc status in prostate tumors.
John Kurhanewicz (UCSF, USA) 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; simultaneously image tumor metabolism and microenvironment; and study response to ADT and treatment resistance.

**New Therapeutic and Diagnostic Approaches**

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

i) **OGX-427** targets heat shock protein Hsp27 whose production is induced by cellular stresses such as chemotherapy, radiation, and hormone therapy. Martin Gleave (University of British Columbia, Canada) demonstrated the interaction of Hsp27 with AR in prostate cancer models, resulting in the enhanced expression of AR-regulated genes. Randomized Phase 2 evaluation of OGX-427 demonstrated that 71% of patients were progression-free at 12 weeks compared to 48% in the control arm. 47% of patients who received OGX-427 plus prednisone experienced a >50% decline in 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.

ii) **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 $^{16}$F-FDHT, and induces tumor regression in hormone-sensitive and
treatment-resistant animal models. Richard Heyman (Aragon Pharmaceuticals, USA) presented an interim analysis of a Phase II study conducted with ARN-509 in three CRPC cohorts: non-metastatic (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 out of eight patients (63% ORR) with measurable disease at baseline in the treatment-naïve metastatic CRPC cohort achieved a partial response according to RECIST.

iii) uPAR (urokinase Plasminogen Activator Receptor) 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, USA) presented the development of two novel agents targeting the uPA axis: 1) ATN-291, a monoclonal antibody that targets uPA and exhibits anti-tumor 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. 2) 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.

iv) Marc Diamond (Washington University, USA) presented results for the activity of pyrvinium, an intestinal parasite inhibitor, and its derivative, tetrahydopyrvinium (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.

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

vi) Amina Zoubeidi (Vancouver Prostate Centre, Canada) reported that enzalutamide activates Her2 which activates MAPK and AKT signaling. Preclinical combination therapy with enzalutamide and Lapatinib, a Her-2 inhibitor, showed promising inhibition in animal models and delayed the onset of enzalutamide resistance. These studies provide proof-of-concept that AR co-targeting is a promising strategy to control therapy resistance.

vii) Scott Dehm (University of Minnesota, USA) 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.

viii) William Redmond (Providence Portland Medical Center, USA) presented preclinical results of combination immunotherapy with OX40 and CTLA-4 monoclonal antibodies. This combination therapy caused potent anti-tumor immunity in prostate cancer models and deserves clinical evaluation.
ix) Haydn Kissick (Harvard University, USA) 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 prostate cancer patients.

x) Brian Olson (University of Wisconsin, USA) presented Phase I results of a DNA vaccine against PAP (Prostatic Acid Phosphatase) in 22 biochemically recurrent prostate cancer patients. 8/22 patients had long-term immune responses to PAP, and presented a novel population of regulatory T-cells which were PAP-specific, CD8+CTLA-4+ and secrete immune suppressing IL-35. The presence of these novel, PAP-specific Tregs can serve as a biomarker to identify patients likely to respond immunologically to vaccination.

xi) Nora Navone (University of Texas, USA) demonstrated 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.

xii) Peter Kuhn (Scripps Research Institute, USA) described the development of a ‘fluid biopsy’ approach that identifies CTCs (without employing traditional cell surface protein-based enrichment) in patient blood samples. This enrichment-free 'High Definition-CTC' assay detects >5 HD-CTCs per mL of blood in 80% of patients with metastatic prostate cancer. Temporal
CTC characterization of a prostate cancer patient revealed the evolution of cancer cells during treatment, demonstrating that ADT and abiraterone alter AR expression.

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.

Josh Lang (University of Wisconsin, USA) presented the microfluidic VerIFAST (Vertical Immiscible Filtration Assisted by Surface Tension) platform for integrated molecular CTC analyses. This system allows cell sorting, capture and purification; live cell intracellular and extracellular staining; and, proteomic and genomic analyses. The VerIFAST platform holds diagnostic and prognostic potential for prostate cancer patients.

**mRNA Translation in Cancer**

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

1. eIF4E (eukaryotic translation initiation factor 4E) is dysregulated in several cancers. Nahum Sonenberg (McGill University, Canada), who discovered the eIF4E protein ~30 years ago and has since studied its complex mechanism of action in cancer, demonstrated that phosphorylation of eIF4E by Mnk1 and Mnk2 (MAP kinase-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.
ii) Kevan Shokat (UCSF, USA) described rational polypharmacology which employs a combination of synthetic medicinal chemistry, kinome 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’ (or off-target kinases).

Clinical Classification of Prostate Cancer

Christopher Logothetis (University of Texas, USA) 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 four 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 two 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, USA) 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 six, i.e. results claimed in only 11% of 53 studies stood up to the original assertions.

S. Stanley Young (National Institute of Statistical Sciences, USA) 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 >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 employing 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, i.e. researchers and epidemiologists who conduct and analyze observational studies as they are responding to current incentives, publications and grants. Therefore, the managers, i.e. 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, such 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 on mechanisms of treatment resistance; the role of field cancerization and tumor microenvironment; determining intratumoral heterogeneity and its impact on precision medicine are important and warranted. The androgen receptor 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 two years have seen great progress in the treatment of CRPC. 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.

Acknowledgements

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References:
1. A comprehensive summary of the research presented and the meeting agenda can be viewed at www.pcf.org/2012RetreatReport.
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