CLINICAL AND TRANSLATIONAL PROSTATE CANCER RESEARCH: ADVANCING TEAM SCIENCE

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To conduct comprehensive and collaborative prostate cancer research for the improvement of screening, prevention, and treatment of patients afflicted with prostate cancer and to reduce racial disparities in prostate cancer morbidity.
Multidisciplinary Team Science

- Created in July 2007
- KCI and HFH
- Monthly meetings
- 45 active members

- Dept. of Oncology
- Dept. of Pathology
- Dept. of Urology
- Dept. of Radiation Oncology
- Dept. of Pharmacology
- Center for Molecular Medicine and Genetics
- Bioactive Lipids Research Program
- Dept. of Electrical Engineering

Barbara Ann Karmanos Cancer Center
Henry Ford Medical Group
Wayne State School of Medicine
Programs and Cores Involved in the PCRT

**Programs**
- Molecular Therapeutics
- Tumor Microenvironment
- Population Studies and Disparities
- Molecular Imaging and Diagnostics

**Cores**
- Biostatistics
- Clinical Trials Office
- Pharmacology
- Biorepository
- Genomics
- Behavioral and Field Research
- Epidemiology Research
- Microscopy, Imaging and Cytometry Resources
PCRT Member Benefits

- Inform Prostate Research Community at KCI and HFH of each other’s areas of interest and research
- Provide scientific environment to foster team science
- Provide constructive feedback on scientific strategies to increase success rate in obtaining new grants
- Encourage translational efforts within areas of expertise such as inflammation, metabolic syndrome, and metastasis
- Improve local and national visibility of prostate cancer research at KCI and HFH
PCRT Successes

2002-2007

- 390 grant applications (R01, R21, K07, DOD, ACS)
- 113 grants funded
- 10.6 million dollars awarded

2007-2012

- 504 grant applications (R01, R21, K07, DOD, ACS, P20, K12, P50, PCF, multi-PI R01, NIDDK)
- 96 grants funded
- 15.3 million dollars awarded

Courtesy of Valerie Wade
PCRT Successes 2013

- DOD, Bock, Cathyn, “MicroRNA in Prostate Cancer Racial Disparities and Aggressiveness.”
- ACS, Xu, Jingping, “Why Don’t Men with Low-Risk Prostate Cancer Choose Active Surveillance?”
- DOD, Chinni, Sreenivasa, “Uncarboxylated Osteocalcin and Gprc6a Axis Produce Intratumoral Androgens in Castration Resistant Prostate Cancer.”
- DOD, Podgorski, Izabela, “Targeting HO-1/FABP-4/IL-1 beta axis in Metastatic Pca.”
General Overarching Challenges

- Reduction of disproportionate burden of prostate cancer (PCa) among AA men
- Identification of aggressive vs indolent prostate cancer
- Developing effective agents against aggressive disease
Focused Overarching Challenges

- Can we identify factors contributing to higher incidence, morbidity, and mortality in AA men with PCa?
- Are there differences in the host biology that may influence response to therapy? Or marker behavior?
  - Immune responsiveness
  - Inflammation
  - Genetic
Projects Identifying Factors Contributing to Aggressive PCa

- Influence of metabolic syndrome on PCa progression and risk of recurrence in AA and EA men (Powell, Beebe-Dimmer)
- Cathepsin K as link between obesity, inflammation and Pca (Podgorski)
- Mechanistic role of miRNAs and their targets in PCa aggressiveness (Sarkar, Sakr)
- Role of thromboxane, 12-LOX and 12-HETE in PCa progression (Honn)
- Role of histone demethylase GASC1 in promoting PCa progression (Yang)
Projects Identifying Factors Contributing to Aggressive PCa

- Novel signaling pathways mediated by PSA, pTEN, and galectin-3 during PCa progression (Raz, Balan)
- Oxidative stress, antioxidants and racial disparities in PCa (Bock)
- PDGF-D and PCa bone metastasis (Kim, Bonfil)
- MT1-MMP/RANKL/RANK axis in PCa bone mets (Fridman, Cher)
- Novel ERG regulation of CXCR4 in PCa progression (Chinni)
- A new approach to targeting AR signaling axis in PCa (Ratnam)
Projects Identifying Novel Therapeutic Targets (Bench to Bedside)

- Novel targets of indoles in PCa (Sarkar) (2R01CA108535-05A1)
  - Phase I of BR-DIM in PSA relapse, non-metastatic, CRPC patients (2979)(Heath)
  - Phase II of BR-DIM in pre-prostatectomy patients (2007-128)(Heath)

- Therapeutic potential of maspin in Pca (Sheng) (3R01CA084176-07S2)(R01 submitted)
  - Phase II of geldanamycin in metastatic CRPC (2891) (Heath)
  - Phase II of ganetespib in metastatic CRPC (2010-070)(Heath)
Projects Identifying Novel Therapeutic Targets (Bench to Bedside)

- PDGF-D and PCa bone metastasis (Kim), MT1-MMP/RANKL/RANK axis in PCa bone mets (Fridman, Cher, Bonfil) (NOMIC W81XWH-11-1-0500)(multi-PI R01 submitted)
  - Relationship of Circulating Tumor Cells (CTC), metastatic tumor tissue and clinical outcome in metastatic PCa (2011-060)(Cher)

- Cathepsin K as link between obesity, inflammation and prostate cancer; potential therapeutic implications (Podgorski, Heath) (NOMIC W81XWH-11-1-0500)
  - Pilot trial of cabozantinib in metastatic, CRPC patients, exploring changes in bone and tumor imaging related pathways (2011-185) (Vaishampayan)
Projects Identifying Novel Therapeutic Targets (Bench to Bedside)

- Galectin-3: a novel marker and therapeutic target (Raz) (R37CA46120-20)(PCF Challenge Award submitted)
  - Pilot trial of galectin-3 in prostate cancer patients (Heath)
  - Phase II of GCS-100 in metastatic, CRPC patients (Heath)
Evaluating differences in tumor biology, specifically regarding immune response in African American (AA) versus European American (EA) men with PCa treated with sipuleucel-T (Lum, Heath)

- Sipuleucel-T is an autologous cellular immunotherapy for the treatment of asymptomatic or minimally symptomatic metastatic CRPC patients
- Three Phase III trials of sipuleucel-T, suggestion of improvement in overall survival in AA vs EA men
Gene signature from Wallace TA et al. had many up-regulated IFN-related genes in AA tumors, suggesting different immunologic and inflammatory profile.

Integrated genome wide analysis by Rose et al. showed significant over-representation of inflammation and immunobiology related genes in AA vs EA PCa patients.

Powell IJ et al. reported differential gene expression between AA vs EA Pca patients, especially in signaling pathways and functions associated with inflammation and lipid metabolism.

Trial Design

- Immune evaluation study
- KCI, HFH, and Johns Hopkins
- 27 AA and 27 EA patients with metastatic, CRPC
- Primary objective: estimate mean level of each of immune parameters
Immune Profile

Serum Testing

Specific Antibodies by Elisa to:

- PAP, PA2024, PSMA, and PSA

Cytokine/chemokines by Luminex

- IFN, IL-2r, TNF, GM-CSF, IL-4, IL-5, IL-6, IL-8, IL-10, IP10, IL-12, IL-15, IL-17

- chemokines: MIP1, RANTES, IP-10

IgG, IgM, IgA, titers to TT, PPA

Phenotyping

- CD3, CD4, CD8, CD25, CD27, CD56, CD54, CD11b, CD14, CD45RO, CD4RA, CD62L, FOXP3

T cell assays

- IFNγ EliSpots response to PC-3

Antibody Production Assays

- Specific anti-PC-3 In vitro antibody synthesis
Randomized Phase II Screening trial of enzalutamide and LHRH analogue versus combined androgen deprivation in metastatic castrate sensitive prostate cancer (Vaishampayan, Chinni)

- Enzalutamide is androgen receptor (AR) antagonist (5-fold higher binding affinity for AR compared to bicalutamide), prevents translocation of AR to nucleus and prevents binding of AR to DNA and coactivator proteins
Background/Rationale

- The length of CAG repeats on the androgen receptor gene has been reported to be significantly different in association with AA race as compared to EA origin.
- Racial differences have also been found among variants of the genes of the enzymes involved in androgen biosynthesis and metabolism, such as SRD5A2, CYP17, and CYP3A4.
- Growth factors and their receptors, which promote cancer cell growth, are another potential cause of the disparity; both EGFR and EPHB2, show racial differences.
- Differences have also been found among genes regulating cell apoptosis, such as BCL2, which is increased in PCa in the AA population.
Trial Design

- Randomized metastatic CSPC patients to receive either: LHRH analogue and enzalutamide or LHRH analogue and bicalutamide
- Stratification by race and bone pain
- Primary objective: to assess the rates of achieving PSA remission
- Correlative biomarkers: expression of key enzymes contributing to intratumoral androgen biosynthesis (SRD5A2, CYP17, CyP3A4, AKR1C3, HSD17b6)
Current Projects Exploring Differences in Host Biology Influencing Therapeutic Response (3)

- Targeting the prostatic tumor microenvironment with PLX3397 (Plexxikon), a tumor-associated macrophage (TAM) inhibitor in men with high risk PCa treated with radiation and ADT (Maier, Heath, Podgorski, Hilman, Beebe-Dimmer)
  - Selective co-inhibitor of FMS (CSF-1R), Kit, and FLT3-ITD
  - Macrophages attractive target: no malignant mutations, stable genome, less likely to develop drug resistance
Chronic inflammation contributes to PCa tumorigenesis

TAM - major component of leukocyte infiltrate into tumor and increase in intra-tumoral macrophage density associated with poor prognosis in PCa

Promotion of tumor growth by macrophages via accelerated intra-and extra-tumor angiogenesis demonstrated in rat model of PCa

Inhibition of MCP-1 (CCL2) shown to prolong survival in PCa bearing mice

Background/Rationale

- Macrophages contribute to tumor radioprotection
- TRAMP-C1 tumors treated with RT show accumulation of TAMs in chronic hypoxic areas from RT
- TAMs may contribute to future regrowth of PCa
- Data support targeting macrophages in the microenvironment as a radiosensitizing strategy in combination with RT
- Xu et al. reported that RT in combination with PLX3397 in RM9 prostate tumors implanted into C57B16 mice results in the smallest tumor size compared to either treatment alone

RM-9 Orthotopic Tumor Growth: Prostate tumors treated with 12 Gy RT ± PLX 3397

Prostate Tumors

Prostate Tumor Volume (mm³)

Con  Con + PLX  RT  RT + PLX

Treatment

Courtesy of Drs. G. Hilman and I. Podgorski
Preliminary Data

• **TUMOR GROWTH**
  
  • PLX3397 caused enhanced tumor growth inhibition induced by high dose RT tumor irradiation: Effect seen both on RM-9 s.c. and prostate tumors
  
  • Histology: RT+PLX caused decreased density of tumor cells, increased fibrous stroma and formation of vacuolated giant tumor cells with degenerative changes and large necrotic areas.
  
  • IHC: Increase in neutrophil infiltration observed with RT is reduced by RT+PLX

**Macrophage markers:** F4/80: Trend to decrease with RT+PLX and increase with RT
  
  • M1 anti-tumor Macrophages NOS2: Dramatic increase >20 fold with RT+PLX at early time points of therapy D6-13, suggesting a switch to M1 type into tumors.
  
  • M2 tumor promoting Macrophages could be decreased by RT+PLX
    
    • MGL1: Trend to decrease with RT+PLX and increase with RT
    
    • ARG1: Fluctuations

**Neutrophils/Granulocyte markers:**
  
  • MPO: Decrease with RT+PLX at early time points of therapy D6-13, but increase with RT.
  
  • Gr-1: Trend to increase with time
**Trial Design**

- ADT, PLX3397 for 6 months, RT at 79.2 Gy
- Phase I, dose-escalation trial using 3 preselected dose levels of PLX 3397
- Prostate biopsy at start of treatment and at beginning of month 5

**Secondary objectives**
- Macrophage markers: CD68
- TAM markers: CD163, CD301(MGL1), IL-10, IL-13, CCL17, CCL22, Dectin-1
- Inflammatory markers: CCL2, CCL7, IL-6, IL-8, TNFa
- Metabolic syndrome markers: weight, hypertension, HgbA1c, glucose, insulin, HDL and LDL cholesterol
Current Projects Exploring Differences in Host Biology Influencing Therapeutic Response (4)

- A Phase II Biomarker Study of Preoperative ASG-5ME monotherapy followed by radical prostatectomy in patients with locally advanced Pca (Cher, Heath)
  - ASG-5ME-fully human monoclonal antibody conjugated to cytotoxic agent MMAE for novel target AGS-5
  - KCI GU team recently completed preoperative pre-prostatectomy study with BR-DIM
Background/Rationale

- Patient options for novel therapy expanding, but therapeutic selection based on an “all-comers” approach.
- Evaluation of tissue and blood from castrate resistant PCa patients limited.
- Biomarker development potentially more successful when there is greater understanding of drug effect on primary prostate tumor.
Trial Design

- Locally advanced Pca patients undergoing surgery
- Identified to have > 3mm Gleason pattern 4 or 5 on one or more needle biopsy cores
- 30 patients receiving one dose of ASG-5ME
- Tissue and blood samples from radical prostatectomy
- Unfortunately, Phase I studies in metastatic, CRPC patients had too many toxicities
- Current neoadjuvant concept discontinued
The PCCTC’s mission is to design, implement, and complete hypothesis-driven phase I and phase II trials of novel agents and combinations that could prolong the lives of patients with prostate cancer.
Core business areas focus include:

- Co-development with sponsors
  - Enhancing the value added to both sponsors and participants
- Investigator initiated research
  - Centralized development and management of trials
- Trial design optimization
  - Standardized entry criteria, endpoints, and outcome measures
- Partnering with industry service organization
  - Leverage subject matter expertise while staying out of the core CRO business
Prostate Cancer Therapeutics Circa 2012: A Changed Landscape As Six Phase 3 Trials Show a Survival Benefit

**Noncastrate**
- Clinically Localized Disease
- Rising PSA

**Castration resistant**
- Clinical Metastases: Noncastrate
- **Non-Metastatic CRPC**
- Castration Resistant Metastatic Pre-Sipuleucel-T 2010 Abiraterone 2013
- Castration Resistant Metastatic 1st-Line Docetaxel 2004
- Castration Resistant Metastatic Post-Cabazitaxel 2010 Abiraterone 2010

**Treatments**
- Alpharadin 2013
- Enzalutamide 2011
Minority Accrual to Prostate Cancer Clinical Trials

- Applicability of clinical and translational advancements to AA men with prostate cancer unknown
- Small percentage of cancer patients enroll in clinical trials, even smaller percentage of AA men with PCa enroll
- KCI has 40% participation of AA men annually in prostate cancer clinical trials within PCCTC
- Other 12 sites average 11% participation of AA men annually
Increasing Minority Participation in Prostate Cancer Clinical Trials

- Current project by Drs. Eggly, Penner, and Manning submitted as R01 (along with Johns Hopkins investigators)
- Overall goal of proposal is to significantly improve rates of decisions by AA men with prostate cancer to participate in clinical trials
- Objective will be achieved by conducting and determining the effect of theory-based, inter-related interventions focusing on patient and oncologist attitudes and beliefs and their communication related to trials
- Future plans include exporting interventions to PCCTC sites
Increasing Minority Participation in Prostate Cancer Clinical Trials

- Planned proposal in line with objectives of the Southeast Michigan Partners Against Cancer (SEMPAC) (U54 CA153606) (Albrecht, Chapman)
- SEMPAC brings together 22 active community based organizations to reduce and eliminate Pca health disparities in older, underserved AA men
- Challenges in our community include 47% functionally illiterate adults, high school graduation rate of 65% and unemployment rate of 10.3%
Summary

- PCRT members are dedicated and committed to advancing team science
  - In days of shrinking budgets and limited grant funding, we have human capital, which is priceless

- Prostate cancer research at KCI is focused on reducing health disparity gap
  - Identify factors contributing to higher incidence, morbidity, and mortality in AA men with Pca?
  - Identify differences in the host biology that may influence response to therapy? Or marker behavior?
Next Steps

- Continue to conduct solid, exciting research in the laboratory and clinic
- Maintain strong and respected local and national presence by strengthening patient advocacy and involvement in Detroit community
- Continue to maintain successful PCRT infrastructure by involving members of KCI Program and Cores
Next Steps

- Focus on grant applications
  - R01, R21, DOD, ACS, PCF
  - P50, multi-PI R01s

- Develop junior faculty projects to maintain rich pipeline and continued mentorship within PCRT

- Continue to collaborate with other expert institutions to advance novel therapeutics and target identification