UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

M.D.L. NO. 1430
CIVIL ACTION NO. 01-10861

IN RE LUPRON® MARKETING AND
SALES PRACTICES LITIGATION

MEMORANDUM ACKNOWLEDGING THE RECEIPT AND REVIEW OF THE A. DAVID MAZZONE THIRD ANNUAL RESEARCH AWARDS PROGRESS and ACCOUNTING REPORT #7

December 22, 2014

STEARNS, DJ.

The A. David Mazzone Research Awards Program is reaching the end of a fourth year of medical investigation dedicated to finding a cure for prostate cancer.[1] The Mazzone Awards Program was made possible by a cy pres distribution of funds remaining after the satisfaction of individual claims arising from the settlement of a national class action involving overpricing of the prostate cancer treatment drug marketed as Lupron®. *See In re Lupron Mktg. and Sales Practices Litig.*, 677 F.3d 21 (1st Cir. 2012). The Mazzone Awards Program presently supports the work of 137

[1] The Program was established in the memory of A. David Mazzone, who served for twenty-six years as a Judge of the United States District Court of Massachusetts. Judge Mazzone died prematurely of complications of prostate cancer. The Program is also intended to honor the other victims of prostate cancer, many of whom were members of the plaintiff class in the underlying Lupron® litigation.

investigators worldwide who are involved in thirty-eight separate research projects.[2]

On November 10, 2014, Dr. Philip Kantoff of the Dana-Farber/Harvard Cancer Center (DF/HCC), the principal investigator, and Dr. Jonathan Simon, President of the Prostate Cancer Foundation (PCF), and the co-principal investigator, submitted the seventh in a scheduled series of Progress and Accounting Reports for the court's review.[3] The Report covers the period from August 1, 2013, to July 31, 2014. The Report summarizes the research progress and accountings of the current grantees,

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[2] The specified goals of the Program are as follows:

> To direct leftover Settlement Pool funds from Lupron® litigation to research initiatives of merit in prostate cancer and other Lupron®-treatable diseases.
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> To distribute Settlement Pool funds to researchers in prostate cancer and other Lupron®-treatable diseases at the national and local level, and to spur collaborative research between prostate cancer and Lupron®-treatable diseases.
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> To distribute Settlement Pool funds through existing organizational channels that have an established record of successful grant distributions (i.e., those which have advanced the state of knowledge in the grants' stated areas of research).
>
> To increase the power and breadth of research in prostate cancer and other Lupron®-related diseases, by (i) the strategic administration of new and existing funding mechanisms; (ii) expanding current avenues of investigation; (iii) recruiting new talent into the field; and (iv) ensuring that research is relevant to the primary goals of advancing diagnostic, treatment and quality of life options for patients with prostate cancer and other Lupron®-treatable diseases.

[3] Of the current thirty-eight research initiatives, thirty-three are funded by DF/HCC and five by PCF Challenge Awards.

as well as and the highlights of the A. David Mazzone Awards Program Retreat held on May 6, 2014, at the Dana-Farber Cancer Institute. The court had the pleasure of attending the Retreat along with members of the prostate cancer research community.

Table 1 of Report No. 7 lists each of the current Mazzone Awards. They are as follows:

DF/HCC Roster I (August 2011-July 2013)

High Impact

Matthew Freedman (Dana Farber Cancer Institute (DFCI)) - *Functional annotation of prostate cancer risk loci discovered through GWAS*

Career Development

Kathryn Wilson (Harvard School of Public Health (HSPH)) - *Phosphorus and calcium intake, tumor microenvironment and prostate cancer progression*

Disparities Research

Donna Berry (DFCI) - *Enhancing usability of the Personal Patient Profile-Prostate (P3P) for black and Hispanic men*

Nancy Keating (Harvard Medical School (HMS)) - *Understanding racial differences in prostate cancer mortality*

DF/HCC Roster II (August 2012 – July 2014)

High Impact

Levi Garraway (DFCI) - *Defining the spectrum of resistance to androgen ablation therapy in prostate cancer*

Steven Balk (Beth Israel Deaconess Medical Center (BIDMC)) - *Molecular characterization of Gleason 3 tumors that progress to Gleason 4*

Zhe Li (Brigham & Women's Hospital (BWH)) - *Castration-resistant luminal cells in the prostate*

Massimo Loda (DFCI) - *Developing a blood-based metabolomic signature of Gleason score*

Robert Cormack (DFCI) - *Nanoplatforms for localized chemo radiation therapy for prostate cancer*

Lupron-Treatable Diseases and Conditions

Aaron Styer for Jose Teixeira (Massachusetts General Hospital (MGH)) - *Pre-clinical in vivo studies investigating the efficacy of mTOR inhibitors for uterine fibroids*

Elizabeth Henske (BWH) - *Targeting estrogen-dependent mechanisms in lymphangioleiomyomatosis LAM*

Career Development

Julie Batista/nee Kasperzyk (BWH) - *Within-person molecular differences in primary versus metastatic prostate cancer*

Jennifer Rider (HSPH) - *Inflammation and tissue microenvironment as predictors of prostate cancer risk, mortality and therapy response among men with an initially benign TURP*

Disparities Research

Lorelei Mucci (HSPH) - *Estimating the prostate cancer burden attributed to lifestyle and genetic factors among African-American and white men*

Christopher Lathan for Karen Emmons (DFCI) - *Factors influencing willingness to participate in biobanking among Black men with and at-risk for prostate cancer*

Community Outreach

Jennifer Allen (DFCI) - *Engaging African American faith communities in prostate cancer education*

DF/HCC Roster III (August 2013 – July 2015)

High Impact

Karen E. Knudsen (Thomas Jefferson University) - *Co-Targeting AR and ERG to treat advanced prostate cancer*

Mark Pomerantz (DFCI) - *Genome-wide analysis of response to androgen deprivation therapy*

Peter Nelson (University of Washington) - *Targeting androgen receptor bypass pathways*

High Impact Trials

Mary-Ellen Taplin & Elahe A. Mostaghel (DFCI) *Clinical trials assessing mechanisms mediating sensitivity and resistance to enzalutamide*

Project Development

Gregory Verdine (Harvard University) - *Targeting the co-activator of the androgen receptor*

Karen Cichowski (BWH) - *Developing novel targeted therapies for advanced prostate cancer*

Career Development

Jennifer Sinnott (HSPH) - *Impact on prognosis of inter- and intratumor heterogeneity in prostate cancer*

Disparities Research

Jennifer Rider for Lisa Signorello (HSPH) - *Chronic stress and racial disparities in prostate cancer*

Community Outreach

Larissa Nekhlyudov, M.D. (Harvard Vanguard Medical Associates) - *Shared medical appointments: An innovative approach to prostate cancer survivorship care*

PCF Challenge Awards – Roster II (August 2012 – July 2014)

Bert O'Malley, M.D. (Baylor College of Medicine) - *Targeting the p160 steroid receptor coactivators (SRCs) in castration resistant prostate cancer*

Martin Pomper, M.D. (Johns Hopkins University) - P*romoter-driven molecular radiotherapy for prostate cancer*

PFC Challenge Awards – Roster III (August 2013 – July 2015)

Jennifer Wu, Ph.D. (Medical University of South Carolina) - *Synergistic immune and lipid metabolism targeting for metastatic prostate cancer*

The court is satisfied with the financial accounting of the Mazzone Program to date and is pleased with the solid scientific advances made by the individual investigators.

Special insight into the accomplishments of the Mazzone Program investigators was provided by the presentations given by the 2011 and 2012 grantees at the Retreat sponsored by DFCI on May 6, 2014. The Retreat

was hosted by Dr. Edward J. Benz, Jr., the President of the Dana-Farber Cancer Institute, and by Dr. Kantoff. I have attempted to summarize below some of the highlights of the showcased presentations.

Session I: High Impact Awards

1. *Charting the androgen receptor cistrome in human prostate tissue*, Matthew Freedman M.D., Dana-Farber Cancer Institute

Dr. Freedman's clinical interest involves a shift of the traditional focus on genetic to epigenetic molecular studies. The goal of his research is to use ChIP-sequencing technique to learn define how the androgen receptor (AR) functionally interacts with genetic sites across the human genome.

Dr. Freedman evaluated primary prostate tumors and matched normal samples from prostatectomy specimens with more than 70,000 AR binding site. Some were exclusively from tumor tissue, others exclusively from normal tissue, and some expressed in both. The analysis of these AR binding sites identified two different motifs (HOXB13 and FOXA1), which co-localize with AR only in tumors. Dr. Freedman's work revealed remarkable plasticity of the AR program during tumorigenesis, dependent on FOXA1 and HOXB13. Interestingly, mutations in HOXB13 were shown to be related to prostate cancer risk.

2. *Molecular characterization of Gleason 3 tumors that progress to Gleason 4*, Steven Balk M.D., Ph.D., Beth Israel Deaconess Medical Center

Dr. Balk concentrates on the study of early stage localized prostate cancer, with the goal of identifying those tumors with low grade features that are more likely to progress to aggressive stages of the disease. For that purpose, microdissection of the Gleason 3 and Gleason 4 areas is performed within the same tumor and analyzed using exome sequencing (DNA analysis looking at the occurrence of mutations in the protein-coding area of the genome). Additional in-depth analysis of selected relevant oncogenes as well as distinct expression of genes between the two patterns is also performed. To date, several tumors have been identified as confirming clonal mutations in both Gleason 3 and Gleason 4 areas (meaning the

evolution from a low grade to a higher grade tumor). Distinct molecular alterations between low grade and high grade such as loss of PTEN allele and some new mutations have also been observed, as well as biological pathways that have been associated with higher grade tumors.

3. *Characterizing resistance to androgen deprivation in prostate cancer,* Levi Garraway M.D., Ph.D., Dana-Farber Cancer Institute

Prostate cancer is an androgen-dependent disease. Several therapeutic agents targeting the androgen receptor (AR) pathway have been developed to treat the disease. However, different mechanisms of resistance to these agents have also been identified. The goal of Dr. Garraway's research is to identify molecular pathways driving resistance to androgen deprivation therapy through AR-dependent and AR-independent mechanisms.

Dr. Garaway identified several new genes of interest using loss of function RNAi screens as drivers of androgen resistance in prostate cancer cell lines. Among them, loss of inositol phosphatase INPP5A, a potential tumor suppressor gene, and loss of PLZF, a known tumor suppressor gene, were able to sustain growth even in the absence of androgens. The understanding of these mechanisms of resistance allows the development of agents to attack both androgen receptors and mechanisms of resistance in order to achieve durable responses in patients with advanced form of the disease.

Session II: Student Training, Career Development, Disparities Research

1. *Student Perspective: Prostate Cancer Research,* Irene Wong, Brandeis University, Dana-Farber/Harvard Cancer Center, CURE Program

Inspired by current breast cancer research, Irene Wong has focused her study on GRANULIN (GRN), a protein that promotes tumor growth by converting normal fibroblast (cells of the microenvironment present in normal and tumor tissues) to act as tumor fibroblast (providing a favorable environment for tumor survival and proliferation). Specifically, this protein has been identified to be present in the development of tumors in young patients.

Investigator Wong's work has characterized the relationship between aging and the ability of bone marrow cells to promote tumor growth. This ability might be related to a lower expression of GRN in bone marrow cells, and decreased amounts of GRN at the tumor site, and ultimately to a reduction of fibroblast transformation to "tumor fibroblast."

2. *Analysis of AR signaling in circulating tumor cells in prostate cancer*, David Miyamoto MD, PhD, Massachusetts General Hospital

Cells released by a tumor in the blood stream are rare. If isolated, however, they can be used as a form of "liquid biopsy." Based on a new technology developed at the MGH (CTC-chip), scientists are able to measure AR activity using PSA/ PSMA expression ratio in the CTCs.

Castration sensitive tumor cells are characterized by high PSA and low PSMA expression. On the other hand, castration resistant cells express low PSA and high PSMA. PSA and PSMA levels in CTCs are used by Dr. Miyamoto to measure AR signaling status in "real time" during therapy. Dr. Miyamoto's research suggests a potential role for the measurement of AR activity in CTCs to be used as a predictor of patient response to endocrine therapy.

3. *Prostate cancer genetic variants, molecular alterations and mRNA expression*, Kathryn Penney ScD, Brigham and Women's Hospital

Dr. Kathryn Penney received the A. David Mazzone Career Development Award for her work on prostate cancer risk variants analysis. Dr. Penney compared tumor samples with normal tissue from the same organ in a large number of patients to identify the genetic variants potentially involved in cancer development. To determine the biological mechanism of these variants entails three major potential outcomes: (1) the understanding of the etiology of the disease; (2) finding an explanation of the mechanism driving epidemiologic results; and (3) identifying new treatment and prevention strategies.

The work presented by Dr. Penney correlated genetic variants with the risk of developing prostate cancer. Interestingly, genetic variants are specifically associated with two distinct molecular subtypes of prostate cancer (ERG+

and ERG- tumors). These associations suggest that prostate carcinogenesis may be different for men with different genetic predispositions.

4. *Phosphorus and calcium intake, tumor microenvironment and prostate cancer progression*, Kathryn Wilson ScD, Harvard School of Public Health

High calcium is a potential risk factor for prostate cancer. Dr. Kathryn Wilson, a Harvard School of Public Health epidemiologist, presented data from a health professional follow-up study involving more than 51,000 subjects. In this cohort, questionnaires were directed specifically to diet and lifestyle. In addition, where available, specimens were obtained from patients who developed prostate cancer.

An analysis of proteins related to the bone metastasis mechanism was conducted with primary tumor specimens. This analysis suggested that two proteins [osteopontin and calcium S receptor (CaSR)] are associated with an increased risk of lethal prostate cancer. Questionnaire data was also correlated with protein expressions associated with a high calcium intake. The results support the hypothesis that diet and lifestyle may impact the risk of prostate cancer and its behavior.

5. *Estimating the prostate cancer burden attributed to lifestyle and genetic factors among African-American and white men*, Lorelei Mucci ScD, Harvard School of Public Health

Dr. Lorelei Mucci's work is built on observed disparities in prostate cancer mortality by race and ethnicity. African-American men in the United States have the highest risk of developing prostate cancer, a risk sixty times greater than men in low risk countries (such as Japan and China). Moreover, they are 1.6 times more likely to be diagnosed with and 2.4 times more likely to die from prostate cancer than white men in the United States. Even when adjustments for differences in access to treatment and care are made, marked disparities remain.

The use of three large cohort studies' datasets were used by Dr. Mucci to assess the different risk factors associated with prostate cancer in African-American men. Significantly, 7 out of 10 factors were more pronounced in African-American than for white men, including obesity and low vitamin D intake. Lifestyle and genetic risk factors associated with prostate cancer

may explain a substantial portion of the differing incidence and mortality or prostate cancer among white men. Dr. Mucci's work raises additional concerns about future patterns of prostate cancer mortality among Hispanic men given trends of increasing obesity, vitamin D deficiency, and lower levels of physical activity.

Session 3: Prostate Cancer Foundation Awards

1. *Imaging biomarkers of treatment response using NaF PET/CT imaging: a prostate cancer clinical trials consortium (PCCTC) effort*, Glenn Liu, M.D., Carbone Cancer Center

Dr. Liu presented the results of his innovative imaging research that can be used to identify and characterize metastatic lesions, and may assist drug development in the treatment of prostate cancer. Since the metastatic disease is very heterogeneous, a quantitative total bone imaging using NaF PET/CT is a promising new tool in evaluating treatment effects by providing a biomarker for treatment responses. In addition, this technology may allow for molecular image-directed biopsies leading to a better understanding of the biology of the disease and its mechanism of resistance.

2. *Induction of synthetic lethality with epigenetic therapy (ISLET) for systemic treatment of prostate cancer*, William Nelson, M.D., Ph.D., Johns Hopkins Medicine

As previously discussed, epigenetic mechanisms that induce changes in gene activity that are not caused by changes in the DNA sequence hold promise not only for cancer biology discovery, but also for therapeutics. This the focus of the research conducted by Dr. William Nelson at John Hopkins.

The objective of Dr. Nelson's work is to build a therapeutic combination agent that would have the potential to better target prostate cancer cells. The overall idea of this approach is that the modulation of epigenetic mechanisms may enhance the sensibility of a therapeutic compound. This phenomenon has been termed Induced Synthetic Lethality. To further that purpose, Dr. Nelson has investigated the effects of decitabine, a well-known agent used in hematology, and hypomethylates DNA, to inhibit DNA methyltransferase (key enzymes involved in epigenetic regulation). When

used at low dose, this agent may prove to be a promising epigenetic therapy.

3. *Promoter-driven molecular radiotherapy for prostate cancer*, Martin Pomper, M.D., Ph.D., Johns Hopkins Medicine

Targeted nanoparticles have the potential to overcome the toxicity and efficacy limitations associated with traditional cytotoxic agents and molecularly targeted drugs by releasing drug directly to cancer cells. Dr. Pomper presented results of experiments with the next generation of radiopharmaceutical compounds for detecting and guiding treatment in prostate cancer.

4. *Targeting the p160 steroid receptor coactivators (SRCs) as a novel approach for the treatment of castration resistant prostate cancer*, Bert O'Malley, M.D., Baylor College of Medicine

The focus of the work presented by Dr. Bert O'Malley was the p160 steroid receptor co-activator 2 (SRC2). SRC-2 is a key protein for metabolic regulation of energy/lipids. SRC-2 also plays a role in cancer: it has been previously demonstrated that its overexpression induces metastasis proliferation, and on the contrary, its deletion inhibits PC metastasis in mouse models. SRC-2 activity in cancer is related to its ability to enhance lipid (energy) production in early metastatic cells by regulating glutamine-dependent lipogenesis. The next step in Dr. O'Malley's work is to investigate SRC-2 as a potential target in cancer.

CONCLUSION

The court lauds the solid scientific and medical research work being conducted under the oversight of Dr. Kantoff and Dr. Simons and the stewardship they have exercised over the funds made available through the Mazzone Awards Program. These have been distributed in innovative ways that have reached out to the larger medical community. The court notes that the next progress report is due March 30, 2015.

/s/ Richard G. Stearns

UNITED STATES DISTRICT JUDGE