



Newsletter of the DF/HCC Kidney Cancer Program

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From the Program Director

By Michael B. Atkins, MD, Beth Israel Deaconess Medical Center, Leader, DF/HCC Kidney Cancer Program

The last few months of 2007 witnessed the Kidney Cancer Program move forward on several important fronts ranging from basic science discovery, to translational and clinical research to patient education and development efforts. Several of these activities are highlighted in the articles and announcements in this Newsletter. Perhaps the major accomplishment of the fall, however, was the coordination and submission of the DF/HCC Kidney Cancer SPORE grant competitive renewal application. Fully 1 year in gestation, the grant weighed in at slightly over 800 single-spaced pages, excluding appendix material. As with the initial SPORE grant, the renewal application included investigators from all the Harvard affiliated hospitals as well as the Harvard School of Public Health and featured five major projects: 1) Clinical Correlations of WTX Inactivation in Wilms Tumor, led by Drs. Dan Haber and Allison Friedman from MGH, 2) Validation of RCC Biomarkers for Early Disease Detection and Response to Targeted Therapy, led by Drs. Othon Iliopoulos, Steve Skates, Doug Dahl from MGH and Chris Wood from MD Anderson Cancer Center in Houston; 3) Acquired Resistance to VEGF Receptor Blockade: Underlying Mechanism and Therapeutic Options, led by Drs. Nahum Goldberg, James Mier and myself from BIDMC; 4) Targeting the PI3-Kinase/ Akt Pathway in RCC: Mechanism of Action and Opportunities for Rational Combination Therapy, led by Drs. James Mier, Pier Paolo Pandolfi and David McDermott from BIDMC; and 5) Adoptive Immunotherapy for Renal Carcinoma Using Dendritic Cell/tumor Fusions, led by Drs. David Avigan from BIDMC and Don Kufe from DFCI. The five projects were integrated by three cores: 1) Administration, Evaluation and Planning Core led by myself with the support of SPORE and Program Administrator Aline Nandelstadt; 2) Biostatistics Core led by Dr. Meredith Regan from DFCI; and 3) Tissue Acquisition, Pathology and Clinical Data Core, led by Dr. Sabina Signoretti from BWH. Description for all projects and cores can be found at: <http://www.dfhcc.harvard.edu/spores/renal/>. The SPORE application also included a description of expanded Developmental Research and Career Development Programs under the leadership of SPORE Co-PIs Drs. Vikas Sukhatme and William Kaelin, respectively. The overall goal of the DF/HCC Kidney Cancer SPORE remains the translation of biological and technological advances into clinically meaningful advances for patients with kidney cancer. The submission of this SPORE renewal application was only possible through the considerable efforts of numerous individuals across the DF/HCC and beyond. The SPORE leadership and I would like to formally thank all those who participated in this effort.

Six new Recipients for 2007 SPORE Developmental Project Awards Announced:

Sabina Signoretti, M.D. (BWH) (2nd year award) Development of mouse orthotopic xenografts of human renal cell carcinoma

David Frank, Ph.D. (DFCI) (2nd year award) STAT-Mediated modulation of HIF signaling: Molecular strategies for the treatment of RCC

David Panka, Ph.D., Daniel Cho, M.D. and James Mier, M.D. (BIDMC) Potential Synergy Between Triterpenoids and NADPH Oxidase Inhibitors in the Treatment of RCC

Vikas Sukhatme, M.D., Ph.D. (BIDMC) LDH-A Inhibitors for the treatment of Fumarate Hydratase (FH) Associated Leiomyomatosis and Renal Cell Cancer (HLRCC)

Michael Zimmer, Ph.D. (MGH) Identification of Novel Proteins that Inhibit HIF mRNA Translation

Towia Libermann, Ph.D. and Vikas Sukhatme, M.D., Ph.D. (BIDMC) Identification of new drugs for treatment of RCC patients using gene signatures and the Connectivity Map database

VEGF Receptor Inhibitor Patient Selection Effort Process

By Toni K. Choueiri, M.D. Dana-Farber Cancer Institute

A growing understanding of the underlying molecular biology of clear-cell RCC, the most common histological subtype in RCC, identified a central role of the von-Hippel-Lindau (VHL) gene in RCC pathogenesis. VHL gene inactivation occurs in over ~60% of sporadic RCC, through a gene mutation or less commonly through promoter methylation. This leads to a defective VHL protein and subsequently to the induction of hypoxia-regulated genes, including potent pro-angiogenic proteins such as vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), Carbonic Anhydrase-9 (CAIX), glucose transporter-1 (GLUT-1), and many others. This understanding of the biology of RCC has fueled the investigation of various VEGF pathway blockers in patients with advanced RCC. Agents such as sunitinib, sorafenib, and bevacizumab have shown significant clinical activity in patients with metastatic RCC who failed cytokines or patients who were previously untreated. Despite these advances, many patients do not benefit

from these therapies and even in patients who respond, the duration of response can be short. Therefore, further investigation of tumor characteristics that might allow for the selection of the patient population that can most benefit from a particular VEGF-targeted therapy is warranted.

Dr. Toni Choueiri, a genitourinary oncologist focused on kidney cancer at Dana-Farber Cancer Institute, will work with colleagues within the DF/HCC Kidney Cancer Program; Dr. Michael Atkins the Kidney Cancer Program leader; Dr. Sabina Signoretti, the Director of the Tissue Acquisition Pathology and Clinical Data Core and Dr. Meredith Regan, the Director of the DF/HCC Kidney Cancer Program/SPORE Biostatistics Core to investigate the predictive value of tumor VHL genotype for predicting tumor response in patients with metastatic renal cell carcinoma who have received sunitinib or

sorafenib as their first tyrosine-kinase (TKI) inhibitor. In addition, they will also look if other factors such as CAIX and GLUT-1 staining, and previously defined pathologic features from Kidney Cancer Program investigations into selection factors for interleukin-2, can further help identify patients who might benefit from these VEGF-targeted agents. Tissue specimens will be collected from consenting patients with kidney cancer who have received either of these VEGF pathway targeted agents at DF/HCC institutions. Specimens will be analyzed for pathologic, immunohistochemical and genotypic factors in the SPORE Pathology Core. Results will be correlated with clinical data including tumor response, PFS and overall survival.

	CAIX low (n=29)	CAIX high (n=57)
RR (partial response)	23%	35%
Median Tumor Shrinkage	-10%	-16%
Median Treatment Duration	5.1 months	9.4 months
Median OS	20.5 months	33.2 months

CAIX Expression predicts for response rate median tumor shrinkage and median overall survival in patients receiving VEGF Target Therapy

Hereditary Leiomyomatosis RCC Research Progress

By Vikas Sukhatme, M.D., Ph.D; and Pankaj Seth PhD., Beth Israel Deaconess Medical Center

Individuals with Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC) develop benign leiomyomas of the skin and uterus as well as particularly invasive kidney cancers. The genetic basis for HLRCC is felt to be a germline inactivating mutation in the gene for the TCA cycle enzyme fumarate hydratase (FH). Since FH is a critical enzyme in the TCA cycle that converts fumarate to malate, it is likely that inhibition of this process will lead to diminished generation of ATP through oxidative phosphorylation. Since the cell requires energy to stay alive, it is reasonable to expect that another energy generating mechanism, known as glycolysis followed by fermenta-

tion will be required to provide both ATP and to maintain what is referred to as redox potential, that is the regeneration in this case of a molecule called NAD+. The pyruvate to lactate conversion step is catalyzed by several lactate dehydrogenases (LDHs) but the LDH-A isoform is up-regulated in tumors. Therefore our goal is to ask whether blockade of this LDH-A enzyme will result in the selective death or at least the inhibition of cell growth of cells in which there is a partial blockade of FH, a situation that arises in patients with HLRCC. In fact, it has recently been shown that FH deficiency leads to upregulation of HIF1 α and that targets for HIF1 such as

LDH-A have been noted to be increased in tumors of patients with FH. Our future goal, a collaboration with Dr. Alan Rigby's group at BIDMC, is to find small molecules that interfere with the activity of LDH-A, thus setting the stage for the development of potential drugs for treating this genetic condition. In addition, such drugs may have wider applicability for treating cancer, since the fermentative step is up-regulated in many tumors.

Calendar

DF/HCC Kidney Cancer Mini Symposium to be held on 06/26/08 at the Dana Farber Jimmy Auditorium from 3:00 to 6:00 pm.

CAIX Imaging Trial To Launch

By Annick Van Den Abbeele, M.D., Dana-Farber Cancer Institute

The majority of renal masses (60%) are discovered incidentally during CT, MRI, or ultrasound imaging. More than half of these renal masses are clear cell renal carcinoma, which is an aggressive phenotype that accounts for 80-90% of all malignant cases and is associated with a worse prognosis than other renal masses. It is important to improve imaging in order to distinguish this subgroup as early as possible to optimize therapy and non-invasively to reduce unnecessary surgery for benign renal masses.

A chimeric antibody (cG250) has been developed that targets a cell surface antigen (CAIX or MN) and has been shown to react with approximately 95% of renal cancers of the clear cell type. In addition to the therapeutic potential, the targeting properties of cG250 to renal clear cell carcinomas make this an attractive agent for imaging renal cell carcinoma. To this end, cG250 has been radiolabeled with ¹³¹I and ¹²⁴I for SPECT and PET imaging and promising results have been shown in early clinical trials.

The Dana-Farber/Harvard Cancer Center will participate in a multi-center Phase II trial sponsored by Willex Pharmaceuticals to evaluate the diagnostic performance of [¹²⁴I]cG250 PET/CT imaging of renal clear cell carcinoma. This trial will enroll patients at the Dana-Farber Cancer Institute, Brigham and Women's Hospital, and the Beth Israel Deaconess Medical Center who have renal masses identified on conventional imaging and are scheduled for surgical routine resection. Patient will undergo pre-operative [¹²⁴I]cG250 PET/CT imaging in addition to the standard clinical care that patients will receive as part of their surgery and related care. Imaging results will be correlated with pathology results. Thus, this trial should provide a definitive evaluation of the diagnostic performance of [¹²⁴I]cG250 PET/CT imaging in identifying CAIX positive clear cell renal cell carcinoma. The trial is led by Dr. Annick Van Debeeel from the Department of Radiology at DFCI and should begin accruing patients in March of 2008.

Patient/Survivor Regional Symposium Held

By David McDermott, M.D., Beth Israel Deaconess Medical Center

On October 26th, 2007, the DFHCC Kidney Cancer Program and the Kidney Cancer Association (KCA) held a joint symposium for kidney cancer patients at the Hyatt Regency in Cambridge, MA. This inaugural event was Chaired by Dr. David McDermott of BIDMC and attended by over one hundred people, both kidney cancer survivors and their family. The symposium was designed to raise awareness about recent breakthroughs in kidney cancer therapy and provide a forum for patients to learn more about the biology and treatment of kidney cancer and about future potential advances in the field.

Symposium faculty included a multidisciplinary group of physicians, nurse practitioners, nurses and social workers for Beth

Israel Deaconess Medical Center, Dana-Farber Cancer Institute and Massachusetts General Hospital.

Highlights of the meeting included: lectures on minimally invasive nephrectomy, recent advances in RCC therapy and novel agents in clinical trials; faculty question and answer sessions and breakout meetings with nursing experts in symptom management and supportive care.

Similar meetings are being co-sponsored by the KCA in a few other cities across the United States. Given the "remarkable success" and general interest generated by this year's Boston/Harvard event, plans are being laid for the 2nd Annual Meeting in October 2008.

Awards/In the News

The Howard Hughes Medical Institute (HHMI) appointed **Daniel Haber, M.D., Ph.D** HHMI investigator for his commitment to basic research discoveries that are translated into improved treatments for patients.

William Kaelin Jr., M.D. (DFCI) SPORE Co-PI was elected to Institute of Medicine, one of the highest honors in medicine.

Vikas Sukhatme, M.D., Ph.D. (BIDMC) SPORE Co-PI was selected as the Chief Academic Officer and Harvard Faculty Dean at BIDMC.

Sabina Signoretti, M.D. (BWH) our Pathology Core Director received a 2007 Partners in Excellence Award by the Partners Student Success Jobs Program Mentors.

Miguel Rivera, M.D. (MGH) received a KO8 from the NIDDK to study the function of WTX in kidney development.

Talia Schwartzberg a 3rd year Hematology Oncology Fellow at **BIDMC** was a finalist for the Annual Presidential Award at the international Society for Biological Therapy of Cancer.

Joint Career Developmental Award with VHL and KCA

The DF/HCC Kidney Cancer Program has entered into agreements with both the VHL Family Alliance and the Kidney Cancer Association to co-sponsor Developmental Project Awards in 2008. Award selections will be made by independent review bodies with representation from the DF/HCC and the collaborating Patient Advocacy Group.

Genentech Fellowship (CDA) Award

Genentech has agreed to sponsor a Career Development Award aimed at supporting a young investigator interested in establishing a career in translational kidney cancer research. The award will provide two years of support with applications due to the SPORE by 04/01/08.

Bob Rebello, a patient advocate for the SPORE, has continued his effort to raise money for Kidney Cancer Research by running Marathons around the world. He has completed his latest marathon in Argentina. You may learn more about his accomplishments by visiting his web site, Bob Rebello's Worldwide Marathons to Raise Money for Kidney Cancer: <http://www.bobrebello.com/>



DF/HCC Kidney Cancer Program Members:

Michael B. Atkins, Leader BIDMC
Othon Iliopoulos, Co-Leader MGH
Seth Leo Alper, BIDMC
David C. Alsop, BIDMC
David E. Avigan, BIDMC
Rupal S. Bhatt, BIDMC
Joseph V. Bonventre, MGH
Deborah Burstein, BIDMC
Daniel C. Cho, BIDMC
Eunyoung Cho, BWH
Sandra L. Dabora, BWH
S. Nahum Goldberg, BIDMC
Daniel A. Haber, MGH
Michelle S. Hirsch, BWH
William G. Kaelin, DFCI
Donald W. Kufe, DFCI
Towia Aron Libermann, BIDMC
Kevin R. Loughlin, BWH
Brendan D. Manning, MGH
Wayne A. Marasco, DFCI
David F. McDermott, BIDMC
M. D. Michaelson, MGH
James W. Mier, BIDMC
Peter Raff Mueller, MGH
Aria F. Olumi, MGH
Meredith M. Regan, DFCI
Neil M. Rofsky, BIDMC
Robert W. Ross, DFCI
Jagesh V. Shah, HMS
Sabina Signoretti, BWH
Steven J. Skates, MGH
Vikas P. Sukhatme, BIDMC
Patrick Yung Chih Wen, BWH
Chin-Lee Wu, MGH
Luiz F. Zerbini, BIDMC

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**Newsletter of the DF/HCC
Kidney Cancer Program**



Current Clinical Trials (for complete list visit our web site at www.dfhcc.harvard.edu/renalcancer)

Advanced Disease

- Vaccination of Patients with Renal Cancer with Dendritic Cell/Tumor Fusions and GM-CSF (DF/HCC 04-117). A Phase II trial for untreated patients who present with metastatic disease and primary tumor in place.
- The High-dose Aldesleuken (IL-2) "SELECT" Trial: A Trial Designed to Prospectively Validate Models of Response to High Dose IL-2 Treatment in Patients with Metastatic Renal Cell Carcinoma (DF/HCC 06-149).
- A Phase II Trial of Perifosine Following Tyrosine Kinase Inhibitor Failure in Patients with Advanced Renal Cell Carcinoma (DF/HCC 06-408).
- Phase II, Randomized trial of continuous Dosing Sunitinib and/or Bevacizumab in Sunitinib-Refractory Patients with Metastatic Renal Cell Carcinoma (DF/HCC 07-202).
- Phase II, Single arm Trial of Combination Sunitinib and Gemcitabine in Sarcomatoid or Poor-risk Patients with Metastatic Renal Cell Carcinoma (DF/HCC 07-212).

- An Open-Label, Phase 2 Study to Evaluate the Efficacy and Tolerability of ABT-869 in Subjects With Advanced Renal Cell Carcinoma (RCC) Who Have Previously Received Treatment With Sunitinib (DF/HCC 07-113)

Adjuvant Therapy

- A Randomized, Double Blind Phase III Trial of Adjuvant Sunitinib versus Sorafenib versus Placebo in Patients with Resected Renal Cell Carcinoma (DF/HCC 06-225).

Laboratory Correlates

- Collection of specimen and clinical data from patients with renal cell carcinoma treated with Target Therapies (DF/HCC 06-105).
- Collection of specimen and clinical data from patients with renal cell carcinoma (DF/HCC 01-130). Tissue banking and database protocol

More News

The Kidney Cancer Program has created Director's Choice Award to assist junior researchers in acquiring preliminary data to support publications and grant submissions. The 2007 recipients were:

Eunyoung Cho, Ph.D. (BWH): Central pathology review of renal cell cancer cases in a large population study of women

Ivan Pedrosa, M.D. (BIDMC): Magnetic Resonance Imaging as a Genomic/Proteomic Expression Correlate to Characterize Renal Cell Carcinoma

Andrew A. Wagner, M.D. (BIDMC): Defining the Radiobiology of Stereotactic Radiosurgery for Renal Cell Carcinoma: Can We Revolutionize the Treatment of Small Renal Tumors?

Contact Information/Donations:

Administrator: Aline D. Nandelstadt
Phone: 617-632-9275 Fax: 617-632-9260
E-mail: anandels@bidmc.harvard.edu