

Winter 2006

In this issue:

- 2 TAPCD Core
- 3 Neoadjuvant Trial Opens
- 3 Research Funding Opportunities
- 3 News & Awards
- 3 Calendar of Events
- 4 Current Clinical Trials

Next Issue Highlights:

- Monitoring Core
- Radio Frequency Ablation
- Vaccine Trials
- Report on April Regional Renal Cancer Symposium



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WOMEN'S HOSPITAL



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GENERAL HOSPITAL



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Harvard School of
Public Health

About the Renal Cancer Program

The Dana-Farber/Harvard Cancer Center Renal Cancer Program brings together a critical mass of investigators and clinicians from across all the Harvard medical institutions to focus their expertise on this disease. With the support of the DF/HCC and the only NCI funded SPORE (Specialized Program for Research Excellence) grant focused on renal cancer, the DF/HCC Renal Cancer Program is in a unique position to optimally explore the many exciting avenues for research in this disease and translate scientific developments rapidly into clinical practice. The Renal Cancer Program conducts basic research into the molecular basis of renal cell carcinoma and clinical investigations across most stages of disease with the goal of identifying biomarkers for early detection and prognosis, novel therapeutic targets, more effective treatments, mechanisms of resistance to current therapies and better ways of predicting whom should receive a particular therapy. Treatment approaches currently under investigation include minimally invasive local treatments, cytokine-based immunotherapies, vaccines and various anti-angiogenic and molecularly targeted agents used alone and in combination.

This research effort is supported by specialized Core laboratories that focus on Tissue Acquisition, Pathology, and Clinical Data; Biostatistics; and Monitoring (Angiogenesis/Immune and Imaging).

Integrating this critical mass of investigators and research projects and disease-directed core activities through the SPORE grant enhances the therapeutic options for our patients. Our goal is not only to conduct great science but to bring new treatments to renal cancer patients in a timely manner.

This newsletter will highlight some of the most promising ongoing basic and clinical research efforts, core services, educational activities, research advances and awards. We hope that you will find this information helpful. We look forward to working with you and hope you will join us in our endeavor.

Sincerely,

Michael B. Atkins, MD
Leader,
Renal Cancer Program



Seated, L-R: Jackie Craigue, Sabina Signoretti MD, Michael Atkins MD, Vikas Sukhatme MD, PhD, James Mier MD
Standing, L-R: David Avigan MD, S. Nahum Goldberg MD, Jacalyn Rosenblatt MD, Meredith Regan PhD, Apryle Seeley, Joyce Graff (VHL Family Alliance), Anne O'Neil, Mauro Mariotti, MD, David Panka PhD, Luiz Zerbini PhD, Towia Libermann PhD, Phil Thayer (HLRCC Family Alliance)

Save the dates!

**Regional Renal Cancer Symposium:
Recent Advances in the Biology and
Treatment of Renal Cell Carcinoma**
April 7, 2006

See calendar section on page 3 for more details.

April Renal Cancer Mini-Symposium
April 27, 2006 • **Speakers: Robert Figlin, MD**, UCLA (oncology); **Eugene D. Kwon, MD**, Mayo Clinic (urology); **Augusto Ochoa, MD**, LSU/HSC (immunology); and **Mark Rosen, MD, PhD**, U. Penn (radiology)

Tissue Acquisition, Pathology, and Clinical Data (TAPCD) Core

By Sabina Signoretti, MD

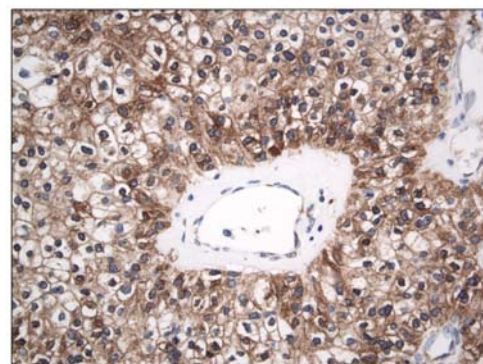
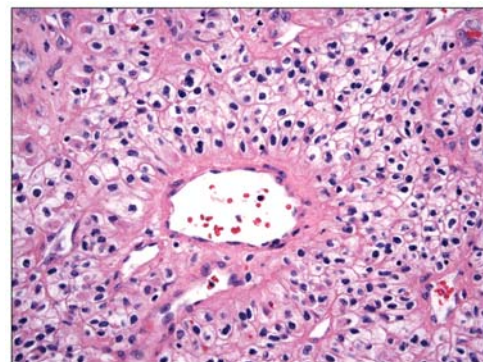
The Tissue Acquisition, Pathology, and Clinical Data (TAPCD) Core has several purposes, the first and foremost of which is to maintain a tissue, blood, and urine repository for the various investigators participating in the Program and SPORE. This task involves the collection, freezing and storage of renal cell carcinoma and paired normal kidney tissue, as well as blood and urine from consenting RCC patients. As of October 2005, frozen tissue is available on 264 patients. In addition, 358 patients have at least one blood sample and 285 patients have at least one urine sample stored in the specimen repository.

The TAPCD Core also maintains a clinical database on all consenting RCC patients. This database, as well as the specimen tracking and secured data management systems, provides an informatics link throughout the participating DF/HCC hospitals which allow for the sharing of clinical outcome data among Program/SPORE investigators.

Another important goal of the TAPCD Core is to provide state-of-the-art histology and molecular pathology services to Program/SPORE Investigators. These services include: routine histology, histopathological evaluation of both human and animal tissues, immuno-histochemistry, in situ hybridization, computer-assisted image analysis, and

generation and interrogation of tissue microarrays. In addition, this Core carries out tissue microdissection, and DNA and RNA preparation for molecular studies. The TAPCD Core also performs mutational analysis of the VHL gene in clear cell RCC specimens stored in the tissue bank.

Since inception, the Core has been collaborating intensively with numerous investigators in the DF/HCC community on research projects related to kidney cancer. As an example, Core pathologists have worked very closely with a group of SPORE investigators headed by Michael Atkins, MD, on a study aimed at identifying molecular correlates of RCC responsiveness to therapy. This study has led to the discovery that expression of Carbonic Anhydrase IX in tumor cells is an important predictor of outcome in RCC patients receiving IL-2-based therapy. Additional studies are currently underway to identify biomarkers predictive of response to novel targeted therapies. Finally, our Core is playing a central role in a project aimed at developing a comprehensive map of renal cancer genetic alterations through systematic analytical methods, including hybridization to high-density SNP arrays. This project is a collaborative effort from several investigators at the Dana-Farber Cancer Institute and the Broad Institute of Harvard and MIT.



Microscopic examination of a clear cell carcinoma of the kidney shows the presence of neoplastic cells with clear cytoplasm and numerous blood vessels (upper panel). Immunohistochemical analysis reveals that tumor cells express high levels of phosphorylated S6, a ribosomal protein that regulates translation (lower panel).

About Our Other Cores

The **Monitoring Core (MC)** serves the translational needs of the Renal Program and SPORE. It consists of three components: an Angiogenesis Monitoring Component (AMC), an Immunologic Monitoring Component (IMC) and an Imaging Component (IC).

Vikas P. Sukhatme, MD, PhD, as Director of the MC provides overall oversight and **James Mier, MD**, and **Neil Rofsky, MD**, are the Co-Directors. The MC was created with multiple components in order to provide maximal flexibility. The AMC performs angiogenic cytokine measurements, endothelial proliferation, mitrigel tube formation and circulating endothelial cell assays. The IMC performs the PBMC isolation and flow cytometry studies to determine the array of adhesion molecules and chemokine receptors expressed. The IC is

responsible for all imaging monitoring of patients participating in the clinical trials with MR and PET, to maximize detection of subtle changes in tumor characteristics.

The **Biostatistics Core** supports all research activities within the Renal Program and SPORE. The Core provides collaboration and consultation on study design, data management/quality control, and data analysis and interpretation to SPORE researchers. Specific aims are to: 1) provide biostatistical collaboration for Program and SPORE Projects, Developmental Projects, and Cores; 2) provide or recommend supporting computational infrastructure and 3) provide consulting and statistical mentoring to Program and SPORE researchers.

Our Clinical Research and Clinical Trials Efforts

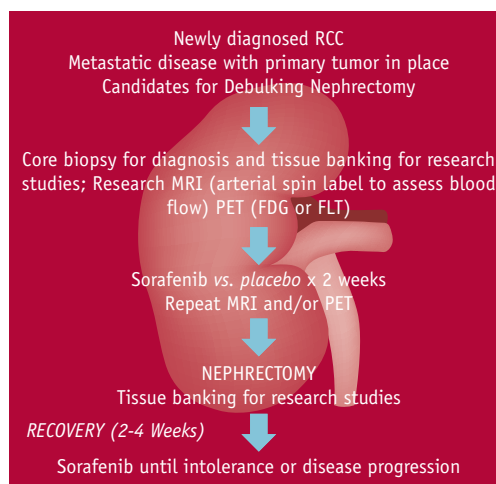
By David McDermott, MD

Over the last three years, DF/HCC investigators have been active participants in several pivotal clinical trials that will lead to the FDA approval of targeted therapies for metastatic renal cancer. We are now exploring ways to combine these novel agents or add them to established regimens, and to improve the selection criteria for systemic therapy in order to improve the outcomes for our patients. Below, Leonard Appleman, MD, PhD, highlights a very important trial for patients presenting with Stage IV disease. More open trials are listed on page 4 and a complete list of trials can be viewed on our website, www.dfhcc.harvard.edu/renalcancer.

Neoadjuvant Trial Opens to Enrollment

By Leonard Appleman, MD, PhD

A Phase II study of BAY 43-9006 prior to and following debulking nephrectomy in patients with metastatic renal carcinoma has opened for enrollment at the DF/HCC. The objectives of this clinical trial are to assess the clinical activity and safety of BAY 43-9006 (sorafenib) before and after surgery in patients diagnosed with metastatic kidney cancer. Subjects will receive sorafenib or placebo for two weeks, up until the night before surgery. After a two-week recovery, sorafenib will be resumed until cancer progression or limiting adverse effects. Arterial spin label MRI and PET scans will be performed to evaluate the ability of these imaging techniques to predict clinical activity early in the treatment period. Subjects will undergo a tumor biopsy prior to starting sorafenib/placebo tablets preoperatively. After surgery, core biopsy specimens will be compared with the corresponding nephrectomy specimens. A series of biochemical and genetic studies will be performed on this material in DF/HCC renal SPORE core laboratories. The study therefore offers a unique opportunity to investigate the mechanisms by which sorafenib exerts its clinical effect in kidney cancer.



Indications for Referral

The Renal Cancer Program provides evaluation and treatment for patients who have been diagnosed with or who have clinical symptoms of renal cell carcinoma.

Those particularly appropriate for evaluation are:

- Patients newly diagnosed
- Patients refractory to current therapy
- Patients eligible for investigational protocols

Patient evaluation will include:

- Detailed history and physical examination
- Comprehensive review of all available pathology specimens and radiologic tests

Based on the findings, physicians develop a customized management plan for each patient.

Awards/In the News

Dr. Pankaj Seth, working in the laboratory of our Monitoring Core Director, **Dr. Vikas Sukhatme**, received one of our first Renal Cancer SPORE Career Development awards to study gene profiling of the renal cell carcinoma endothelium. This year he successfully competed to receive a Howard Temin Award from the NCI and a Developmental Project award from the Renal SPORE.

Dr. Daniel Cho, currently a third year Hematology/Oncology fellow at BIDMC, received two awards this year. An American Association of Clinical Research Barletta Foundation Fellows Grant for Translational Research for a project on predictors of response to targeted therapies in patients with advanced renal cell carcinoma and a Paul S. Carbone Award from the ECOG Foundation.

Research Funding Opportunities

DF/HCC Renal Cancer SPORE

Career Development Awards –

Applications due August 2006

Current Recipients: Dr. Won Han, BWH and Dr. Rob Ross, MGH

DF/HCC Renal Cancer SPORE

Developmental Project Awards –

Applications due August 2006

Current Recipients:

Drs. Miguel Rivera/Daniel Haber, MGH
Drs. David Alsop/Neil Rofsky, BIDMC
Drs. Sabina Signoretti/Holger Moch, BWH
Drs. Jacalyn Rosenblatt/David Avigan, BIDMC
Drs. Luiz Zerbini/Towia Libermann, BIDMC
Dr. Pankaj Seth, BIDMC

Calendar

April 7, 2006 8 am – 6 pm

Regional Renal Cancer Symposium: Recent Advances in the Biology and Treatment of Renal Cell Carcinoma

8.5 CMEs available, 9.1 CEs pending
Marriott Copley Place, Boston, MA

April 27, 2006 3 – 6 pm

Renal Cancer Mini-Symposium

Jimmy Fund Auditorium, Dana-Farber Cancer Institute, Boston, MA

For more information or to register for either symposium, call 617-667-1959.

Patient Connections

A volunteer group of patients, the *Kidney Cancer Patient-to-Patient Network*, is available to provide support to newly diagnosed patients and their families. For more information, contact Susan Graham-McLoughlin, clinical liaison, at 617-667-1930.



DF/HCC Renal Cancer Program Members:

Seth Leo Alper, BIDMC
Len Appleman, DFCI
Michael B. Atkins, BIDMC
David E. Avigan, BIDMC
Joseph V. Bonventre, MGH
Deborah Burstein, BIDMC
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William Hahn, DFCI
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Matthew R. Smith, MGH
Vikas P. Sukhatme, BIDMC
Patrick Wen, BWH



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

Advanced Disease

- A Phase I/II Trial of Sorafenib in Combination with Bevacizumab in Patients with Advanced Renal Cancer. Investigator initiated CTEP sponsored trial of a VEGFR/PDGFR inhibitor (Sorafenib) and a VEGF neutralizing antibody (Avastin) in patients with metastatic RCC. Patients receive escalating doses of these targeted therapies in the Phase I portion of the study.
- Vaccination of Patients with Renal Cancer with Dendritic Cell/Tumor Fusions and GM-CSF. A phase II trial for untreated patients who present with metastatic disease and primary tumor in place. They receive a series of vaccinations using fusions of autologous dendritic cells and tumor cells obtained from the debulking nephrectomy specimen and GM-CSF. (SPORE Project 5)

Adjuvant Therapy

- A Randomized Double Blind Phase III Study to Evaluate Adjuvant cG250 Treatment Versus Placebo in Patients with Clear Cell RCC and High Risk of Recurrence. Industry sponsored, international study of monoclonal antibody therapy to cG250 (Carbonic Anhydrase IX) following nephrectomy for patients in three high risk categories (T3b, T3c or T4 + N0M0, any T and N+ disease, T1b, T2 or T3a + MVI and Grade > 3).

Laboratory Correlates

- Analysis of Discarded Tissue in Patients with Renal Cell Carcinoma Undergoing Either Nephrectomy or Resection of Metastatic Disease. Tumor tissue is stored in our Tissue Bank to be analyzed by gene expression profiling and various immunohistochemical and RT-PCR techniques in an effort to discover new prognostic factors, predictors of response and resistance and new therapeutic targets.
- Collection of Specimen and Clinical Data from Patients with Renal Cell Carcinoma. Tissue banking and database protocol. (SPORE PATH CORE)

Contact Information/Donations:

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