Final Progress Report for Research Projects Funded by Health Research Grants

Instructions: Please complete all of the items as instructed. Do not delete instructions. Do not leave any items blank; responses must be provided for all items. If your response to an item is "None", please specify "None" as your response. "Not applicable" is not an acceptable response for any of the items. There is no limit to the length of your response to any question. Responses should be single-spaced, no smaller than 12-point type. The report **must be completed using MS Word**. Submitted reports must be Word documents; they should not be converted to pdf format. Questions? Contact Health Research Program staff at 717-783-2548.

1. **Grantee Institution:** The Trustees of the University of Pennsylvania

2. **Reporting Period (start and end date of grant award period):** 1/1/2009-12/31/2012

3. **Grant Contact Person (First Name, M.I., Last Name, Degrees):** Gearline R. Robinson-Hall, BSF

4. **Grant Contact Person's Telephone Number:** 215-746-6821

5. **Grant SAP Number:** 4100047654

6. **Project Number and Title of Research Project:** 4 - Validation of Imaging Markers for Use in Cancer Clinical Trials

7. **Start and End Date of Research Project:** 1/1/2009-12/31/2012

8. **Name of Principal Investigator for the Research Project:** Mark Rosen, MD, PhD

9. **Research Project Expenses**.

   9(A) Please provide the total amount of health research grant funds spent on this project for the entire duration of the grant, including indirect costs and any interest earned that was spent:

   $ 226,196.05

   9(B) Provide the last names (include first initial if multiple individuals with the same last name are listed) of **all** persons who worked on this research project and were supported with health research funds. Include position titles (Principal Investigator, Graduate Assistant, Post-doctoral Fellow, etc.), percent of effort on project and total health research funds expended for the position. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name	Position Title	% of Effort on Project	Cost
ROSEN	ASSOC.PROF.	3%YR2; 3%YR4	11,483.28
THOMAS	MGR.RES.PROJ.	4%YR1; 17%YR2; 11%YR4	24,533.89
MYERS	CLIN.RES.MONITORING SPEC.	60%YR2; 2%YR3	34,459.40
STEINGOLD	TECH.DIR.CORE.LAB	50% Yr.1	34,325.38

9(C) Provide the names of **all** persons who worked on this research project, but who *were not* supported with health research funds. Include position titles (Research Assistant, Administrative Assistant, etc.) and percent of effort on project. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name	Position Title	% of Effort on Project
FERRARA	DATA.MANAGER	20%
ENGLANDER	IMAGING.SPECIALIST	20%

9(D) Provide a list of **all** scientific equipment purchased as part of this research grant, a short description of the value (benefit) derived by the institution from this equipment, and the cost of the equipment.

Type of Scientific Equipment	Value Derived	Cost
NONE		

10. Co-funding of Research Project during Health Research Grant Award Period. Did this research project receive funding from any other source during the project period when it was supported by the health research grant?

Yes_____ No____X_____

If yes, please indicate the source and amount of other funds:

11. Leveraging of Additional Funds

11(A) As a result of the health research funds provided for this research project, were you able to apply for and/or obtain funding from other sources to continue or expand the research?

Yes___X_____ No_____

If yes, please list the applications submitted (column A), the funding agency (National Institutes of Health—NIH, or other source in column B), the month and year when the

application was submitted (column C), and the amount of funds requested (column D). If you have received a notice that the grant will be funded, please indicate the amount of funds to be awarded (column E). If the grant was not funded, insert "not funded" in column E.

Do not include funding from your own institution or from CURE (tobacco settlement funds). Do not include grants submitted prior to the start date of the grant as shown in Question 2. If you list grants submitted within 1-6 months of the start date of this grant, add a statement below the table indicating how the data/results from this project were used to secure that grant.

A. Title of research project on grant application	B. Funding agency (check those that apply)	C. Month and Year Submitted	D. Amount of funds requested:	E. Amount of funds to be awarded:
DCE-MRI for Assessment of Vascular Normalization by Nelfinavir in Lung Cancer	■NIH ☐ Other federal (specify:_____) ☐ Nonfederal source (specify:_)	12/2009	$500,000	$408,775
Use of PET and MR Imaging Biomarkers to Predict Response of Renal Cell Carcinoma to Tyrosine Kinase Inhibitor Therapy	☐NIH ☐ Other federal (specify:_____) ■ Nonfederal source (specify: V Foundation__)	2010	$600,000	$600,000

11(B) Are you planning to apply for additional funding in the future to continue or expand the research?

Yes____X_____ No_____

If yes, please describe your plans:

A U01 submission for funding under the NIH program for the Quantitative Imaging Network (QIN) was submitted in February of 2013.

12. Future of Research Project. What are the future plans for this research project?

- Continued growth and expansion of the Clinical Imaging Core, including addition of more technical and IT support to facilitate throughput.
- Addition of PERCIST evaluation of FDG-PET results to the Tumor Response Service.
- Growth and technical development of the Oncologic MRI Core Service.
- Incorporation of advanced PET application (including novel tracer studies) into the CIC to improve access of clinical investigators to new imaging technologies.

13. New Investigator Training and Development. Did students participate in project supported internships or graduate or post-graduate training for at least one semester or one summer?

Yes___X_____ No_____

If yes, how many students? Please specify in the tables below:

	Undergraduate	Masters	Pre-doc	Post-doc
Male				5
Female	1			
Unknown				
Total	**1**			**5**

	Undergraduate	Masters	Pre-doc	Post-doc
Hispanic				
Non-Hispanic	1			5
Unknown				
Total	**1**			**5**

	Undergraduate	Masters	Pre-doc	Post-doc
White	1			1
Black				
Asian				4
Other				
Unknown				
Total	**1**			**5**

14. Recruitment of Out-of–State Researchers. Did you bring researchers into Pennsylvania to carry out this research project?

Yes___X_____ No_____

If yes, please list the name and degree of each researcher and his/her previous affiliation:

Ganesh Adluru, PhD, University of Utah

15. Impact on Research Capacity and Quality. Did the health research project enhance the quality and/or capacity of research at your institution?

Yes____X_____ No_____

If yes, describe how improvements in infrastructure, the addition of new investigators, and other resources have led to more and better research.

Growth of the CIC has provided impetus to spur new research in imaging biomarkers at the University of Pennsylvania Cancer Center.

16. Collaboration, business and community involvement.

16(A) Did the health research funds lead to collaboration with research partners outside of your institution (e.g., entire university, entire hospital system)?

Yes_____ No____X_____

If yes, please describe the collaborations:

16(B) Did the research project result in commercial development of any research products?

Yes_____ No____X_____

If yes, please describe commercial development activities that resulted from the research project:

16(C) Did the research lead to new involvement with the community?

Yes_____ No____X_____

If yes, please describe involvement with community groups that resulted from the research project:

17. Progress in Achieving Research Goals, Objectives and Aims.

List the project goals, objectives and specific aims (as contained in the grant agreement). Summarize the progress made in achieving these goals, objectives and aims for the period that the project was funded (i.e., from project start date through end date). Indicate whether or not each goal/objective/aim was achieved; if something was not achieved, note the reasons why. Describe the methods used. If changes were made to the research goals/objectives/aims, methods, design or timeline since the original grant application was submitted, please describe the changes. Provide detailed results of the project. Include evidence of the data that was generated and analyzed, and provide tables, graphs, and figures of the data. List published abstracts, poster presentations and scientific meeting presentations at the end of the summary of progress; peer-reviewed publications should be listed under item 20.

This response should be a DETAILED report of the methods and findings. It is not sufficient to state that the work was completed. Insufficient information may result in an unfavorable performance review, which may jeopardize future funding. If research findings are pending

publication you must still include enough detail for the expert peer reviewers to evaluate the progress during the course of the project.

Health research grants funded under the Tobacco Settlement Act will be evaluated via a performance review by an expert panel of researchers and clinicians who will assess project work using this Final Progress Report, all project Annual Reports and the project's strategic plan. After the final performance review of each project is complete, approximately 12-16 months after the end of the grant, this Final Progress Report, as well as the Final Performance Review Report containing the comments of the expert review panel, and the grantee's written response to the Final Performance Review Report, will be posted on the CURE Web site.

There is no limit to the length of your response. Responses must be single-spaced below, no smaller than 12-point type. If you cut and paste text from a publication, be sure symbols print properly, e.g., the Greek symbol for alpha (α) and beta (ß) should not print as boxes (□) and include the appropriate citation(s). DO NOT DELETE THESE INSTRUCTIONS.

In the 2011 Annual Report the end date was misreported. Therefore, the activities and findings for the 2012 Annual Reporting period 7-1-11 to 6-30-12 had not been submitted. The activities and findings for this period are noted below, which builds on the report of the prior year, emphasizing progress since last report on two areas of growth in the Clinical Imaging Core (CIC) of the Abramson Cancer Center (ACC) of the University of Pennsylvania: 1) Standardized reporting of routine imaging results, and 2) development of novel methods for analysis of advanced cancer imaging in MRI and PET.

<u>1. Develop an infrastructure to support standardized analysis of images performed on cancer trials at Penn:</u>

There has been continued growth of the CIC since last report. Ongoing areas of development are discussed below.

- Development of a RECIST tumor response lab led by Dr. Rosen
    - Continued infrastructure development has taken place to streamline services and allow for expansion.
- Development of software for on-line request for RECIST analysis by ACC members
    - The web-based order entry system is fully operational and is used by approximately thirty clinical coordinators in the ACC. The Tumor Response Core is a database-driven dynamic website which currently runs on Windows 2008 Server under the University of Pennsylvania Heslth System domain. Cancer center uusers are authenticated through the login screen. The users' accounts are managed by the database administrator and coordinators.
    - Image analysis worklist with order status is generated automatically to facilitate workflow. Turnaround times from report ordering to final results are now tracked automatically by the order entry system

- Development of on-line software tools for tabulating, storing, and reporting RECIST analyses to ACC members
    - Several iterations of data table construction were developed and tested by core lab staff to determine optimal data entry and retrieval for RECIST, WHO, and IR assessment models. A final data table structure has been chosen and implemented in MySQL 5.1 The front-end entry is developed with PHP. We are currently back-populating these data tables with the, results from nearly 1000 imaging events analyzed over the course of the last two years.
- Development of automated imaging analysis tools to streamline the analysis of linear tumor measurements from cross-sectional imaging studies
    - The analysis of automated tools for result reporting is on on-going area of evaluation. In collaborations with Daniel Rubin, MD, PhD of Stamford University and and the American College of Radiology Imaging Network (ACRIN), version 1 of the AIM interface with Oririx was tested, resulting in a reported 23% increase in radiology reader efficiency. Currently, version 2 of the AIM tool, expanded to use via web-based interfaces is ongoing.
- Infrastructure to facilitate protocol review regarding technical and regulatory aspects of all imaging in clinical trial work in the ACC.
    - Developments in the CIC include restructuring of the process for protocol submission and review. Current efforts revolve around the development of a high-level organizational structure that will interface directly with the IRB to identify human clinical trials using research (i.e., non-clinicallly mandated) imaging. As envisioned, this structure will serve as an interface between the IRB and the imaging modality review boards in radiology (MRI, Ct, and PET/SPECT). It is expected that implementation of this system will streamline the process of protocol review, namely by relieving the individual clinical investigators of the need to identify when imaging requirements of clinical trial deviate form the norms of clinical imaging in the Department of Radiology.
- Mechanisms for combined reporting of cross-sectional and bone scan results in prostate cancer patients on clinical trials.
    - Drs. Rosen and Perini of the CIC continue work with Dr. Naomi Haas of the ACC to facilitate integrated reporting of bone scan and CT reports in patients with metastatic prostate cancer.

<u>2. Explore novel approaches to image analysis to improve imaging markers for cancer trials:</u>

In support of the above goals, current funding for the CIC has provided for the development of the following infrastructure for facilitating novel imaging biomarker studies and image analysis for human subjects undergoing clinical trials at the ACC.

- Infrastructure to facilitate project development teams, including key members of ACC programs and imaging experts in radiology, medical physics, and biomedical engineering
    - A web portal to allow Cancer Center members to request radiology collaborators for oncologic imaging biomarker project development is now open. This service will allow the Radiology Department to better track and monitor the scientific imaging needs of the Cancer Center community.

- Establishment of an IND-official and office in the department of radiology to assist in regulatory aspects of protocol development for novel imaging agents
    - In collaboration with Ms. Myers, Kathleen Thomas, administrative director of the Clinical Imaging Core, has completed a study of the performance of a centralized Radiology Department IND office to handle logistics for IND application processing.
- Identification of key individuals in the Molecular Imaging program in the Department of Radiology to develop methods for improved reporting of standard uptake value (SUVs) for individual tumor lesions in FDG-PET studies
    - The Department of Radiology has developed an intiative for standardized reporting of tumor SUV values in clinical FDG-PET exams. This project is tied to the recently inaugurated fellowship training program in molecular imaging.
- Novel methods for quantifying normalized tumor uptake ratios in PET studies using large molecular I-131 labeled radiotracers
    - PET imaging with I-131 labeled cG250 is ongoing in a study of patients with metastatic RCC undergoing therapy with the novel multi-kinase inhibitor, Brivanib.
- Implementation of batch processing and analysis of tumor perfusion and permeability data from dynamic contrast-enhanced (DCE-)MRI studies
    - Volumetric DCE-MRI trial in locally advanced lung cancer has completed accrual of 28 patients. Prelilminary analysis demonstrates a coefficient of variation of approximately 10% for whole tumor K^{trans}. Other trials using volumetric DCE-MRI acquisition in metastatic ovarian and renal cell carcinoma have been completed or are ongoing.
- Methods for determining pixel-wise changes in tumor ADC values from diffusion weighted imaging (DWI) in MRI
    - Version 1 tool in the University of Pennsylvania core laboratory has been developed and tested in early tumor response assessment functional MRI trials invovlging lung and renal cancer. The tool allows for reporting of three-dimensional pixel-wise assessment of tumor diffusion metrics, including apparent diffusion constant (ADC), true tumor diffusion (D_t), and rapid diffusion (i.e. perfused) fractional volume (F_p)
- Initiation of quantitative DCE-CT studies and image analysis
    - The combined GOG-ACRIN trial of DCE-CT assessment of ovarian cancer response to Avastin therapy has opened at the University of Pennsylvania.

Throughout the funding period of this grant, support was provided to establish the Clinical Imaging Core (CIC), a shared resource of the NCI-funded Abramson Cancer Center (ACC) of the University of Pennsylvania. The stated goal of the CIC was to provide support to clinical trial investigators in the use and analysis of basic and advanced imaging techniques to investigate the mechanism of success of traditional and novel anti-cancer therapies in human clinical trials. More explicitly, the goal of the CIC was to provide a portal for entry for clinical investigators to access the various areas of clinical, technical, scientific, and imaging expertise within the Department of Radiology at the University of Pennsylvania. These endeavors were designed to facilitate the integration of both basic and advanced imaging techniques and the derivation of the

imaging results, so as to promote the use of imaging biomarkers in human clinical oncology trials at the University of Pennsylvania.

The project was divided into two main areas of activity, as stated in the project overview from the initial grant application:

> 1. Develop an infrastructure to support standardized analysis of images performed on cancer trials at Penn: The project will develop an operational interface between the cancer center and the radiology department. The approach will employ a dedicated imaging research coordinator with experience in imaging and image management who will coordinate management of imaging data resulting from cancer trials such that they are made available in a centralized 3D imaging laboratory for analysis an interpretation. A cadre of imaging clinical scientists will oversee the analysis according to standardized protocols. This will have the effect of reducing variability in the determination of such endpoints as progression free survival and improve the performance of cancer trials across the Abramson Comprehensive Cancer center.
>
> 2. Explore novel approaches to image analysis to improve imaging markers for cancer trials:
> The extraction of quantitative data from imaging examinations is a critical component of the imaging clinical trial. This activity may include simple geometric measurements made by radiologists, complex reader assessments, semi-automated and automated quantitative analysis which may also include complex modeling. Currently, response and progression on cancer trials is evaluated by measurement of tumor size and assessing growth and shrinking. This analysis does not account for scenarios such as tumor necrosis without significant changes in tumor size, or reduced tumor proliferation. As part of this project, novel approaches to image analysis such as adjusting size for percent necrosis (identified by the absence of contrast enhancement) or dynamic MRI perfusion measurements will be explored. This will involve performing these analyses on patients on trial, and correlating the results against patient outcome (survival, disease free survival). It is anticipated these novel approaches will better correlate with outcome and reduce the number of patients needed to evaluate treatments in future trials.

At the outset of this funding period, we indicated the expected research outcomes and benefits, as stated below from the original funding request:

1. More effective clinical cancer trials at the Abramson Cancer Center: As a result of the coordination and standardization of image analysis, it is anticipated that the data derived from imaging studies will have reduced variability. This will increase the power of trials that utilize imaging endpoints such as progression free survival and response rate. The improvement of effectiveness of the trials utilizing current endpoint will impact a wide range of clinical research performed at the Abramson Cancer Center.

2. Clinical trials based on new imaging biomarkers: The exploration of newer image analysis methods that result in new markers will result in improved endpoint for clinical trials. This is anticipated to result in trial endpoints that will detect response/progression earlier in the course of treatment resulting in quicker trials. This will have a broad impact on the development of newer therapeutics by reducing the clinical trial timeline.

This final report details the establishment of the Abramson Cancer Center Clinical Imaging Core (ACC-CIC, or CIC), as well as the progress made in the two stated goals of the CIC: 1) more effective clinical trial operations via standardized approach to imaging result reporting, and 2) introduction of novel imaging biomarkers into a broader array of clinical trials at the University of Pennsylvania.

A. Establishment and Mission of the Clinical Imaging Core of the Abramson Cancer Center

Aided by the current funding, the ACC-CIC was established in early 2009. Personnel included Mark Rosen, MD, PhD as director, and Chaintanya Divgi, MD, as co-director. Additional personnel included technical leadership from Kathleen Thomas, MS, and Scott Steingall, RT. Shortly after the establishment, Dr. Divgi departed from the University of Pennsylvania, and Dr. Rosen was established as the sole director. The CIC began by advertising its mission of facilitating the conduct of imaging in human clinical oncology trials, and embarked on a period of discovery in meetings with key members of the ACC administration leaders of the Programs and Oncology Divisions at the University of Pennsylvania. With the assistance of Ms. Thomas, a web-site detailing the goals and resource of the core was established and advertised throughout the cancer center.

Throughout the period of funding, the CIC has developed methods of streamlining the regulatory and logistic aspects of imaging in clinical trials. A team of clinical coordinators with expertise in the mechanics of experimental imaging management was trained and made available to members of the Cancer Center. A committee was established to oversee regulatory submissions, and to serve as a liaison between the Cancer Center trial groups and the various modality-specific (i.e. MRI, CT, PET) regulatory committees that review and implemented experimental imaging protocols. Concurrently, Dr. Rosen worked to establish the two main goals of the CIC, improved availability and efficiency in reporting standardized tumor response assessments, and the development of advanced biomarkers of cancer response to modern anti-cancer therapies.

B. Development of the Tumor Response Service (“RECIST core”) within the CIC.

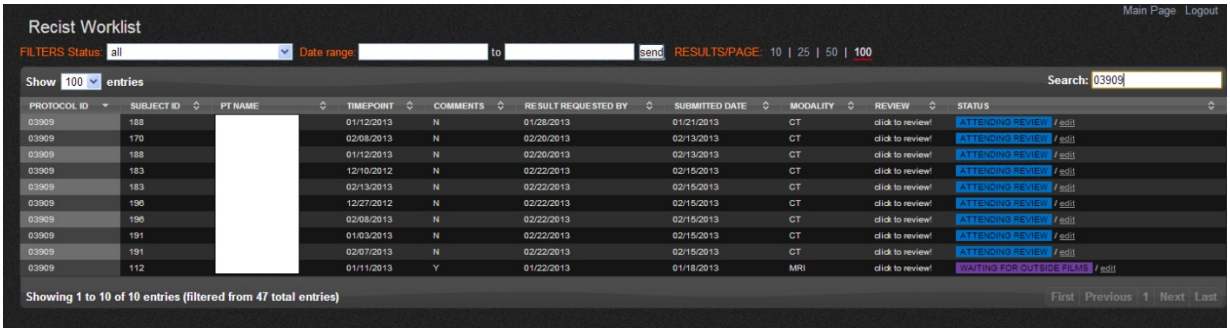
Through direct contact and discussion with clinical oncologic trialists across a spectrum of disciplines in the ACC, it was determined that the translation of routine imaging results from radiology reports into trial-ready tabular results was a key area of clinical trial operations requiring burdensome use of personnel resources (including administrative and professional). The areas of the ACC most affected by this process were the Developmental Therapeutics Program (DT, responsible for phase I and early-phase II trials) and the Clinical Research Unit (CRU, responsible for late phase II and phase III clinical trials). The CRU itself encompassed late phase trials in a number of ACC Programs and clinical trial divisions, including breast

cancer, melanoma, thoracic malignancies, GI cancers, GU cancers, and gynecologic cancers.

Following these informal surveys, the medical and technical leaders of the CIC undertook a needs assessment and resource evaluation within the Department of Radiology. Through these endeavors, it was determined that a parallel image result reporting structure in the radiology department was feasible through integration of existing hardware, software, servers, and user interfaces for image presentation and longitudinal tracking of image annotation. From these components, the tumor response service was developed, housed within the pre-existing Department of Radiology 3D Core Laboratory.

Beginning in September, 2009, the Tumor Response Service of the CIC began operations. Services were initially advertised as word-of-mouth among oncology trial groups. Costs were covered entirely through external funding. Reporting was done on paper, and results were conveyed from manually scanned documents via email. As the service demand grew, it became apparent that a more comprehensive tracking system was required to ensure that all requested results were completed and transmitted to the clinical trial groups in a timely manner. This need became even more acute as it became apparent that the results from the Tumor Response Core were begin used for real time clinical decisions of patients under therapy, and not simply for retrospective confirmation and documentation of RECIST results for reporting to trial sponsors.

In response to these needs and the growing demands, we began the development of a web-based data entry and tracking system. This was initiated through information technology specialists in the Department of Radiology, who implemented a formal database regarding all attributes of research protocols, enrolled subjects, and imaging time points. The project was developed using MySQL 5.1, with front-end entry developed with PHP. Once achieved, this technical advance created a graphic work list, updated hourly, for the user to determine needed work of the day. An example display is shown below:



The introduction of the web-based order entry has markedly improved efficiency in the Tumor Response Core. Further efficiencies are expected as we finalize web-based tumor measurement entry, and complete staff training. At that time, the role of the radiologist will be limited to the following:

- review new protocol submission to confirm expected imaging and tumor response method (e.g. RECIST 1.1, irRC, etc.)
- perform initial target and non-target measurements
- confirm follow-up measurements and reporting by core lab technical staff.

Under this model, radiologist time is estimated at approximately 10 minutes per time point.

Currently, result data is housed in separate data tables (upgrades to the MYSQL 5.1 database in progress will merge these result tables with those from the primary archive, allowing for automated generation of subject status based on the prevailing tumor response model). This archiving of tumor data allows for generation of structured result tables, which are then forwarded to the trial coordinator for archiving as a case report form:

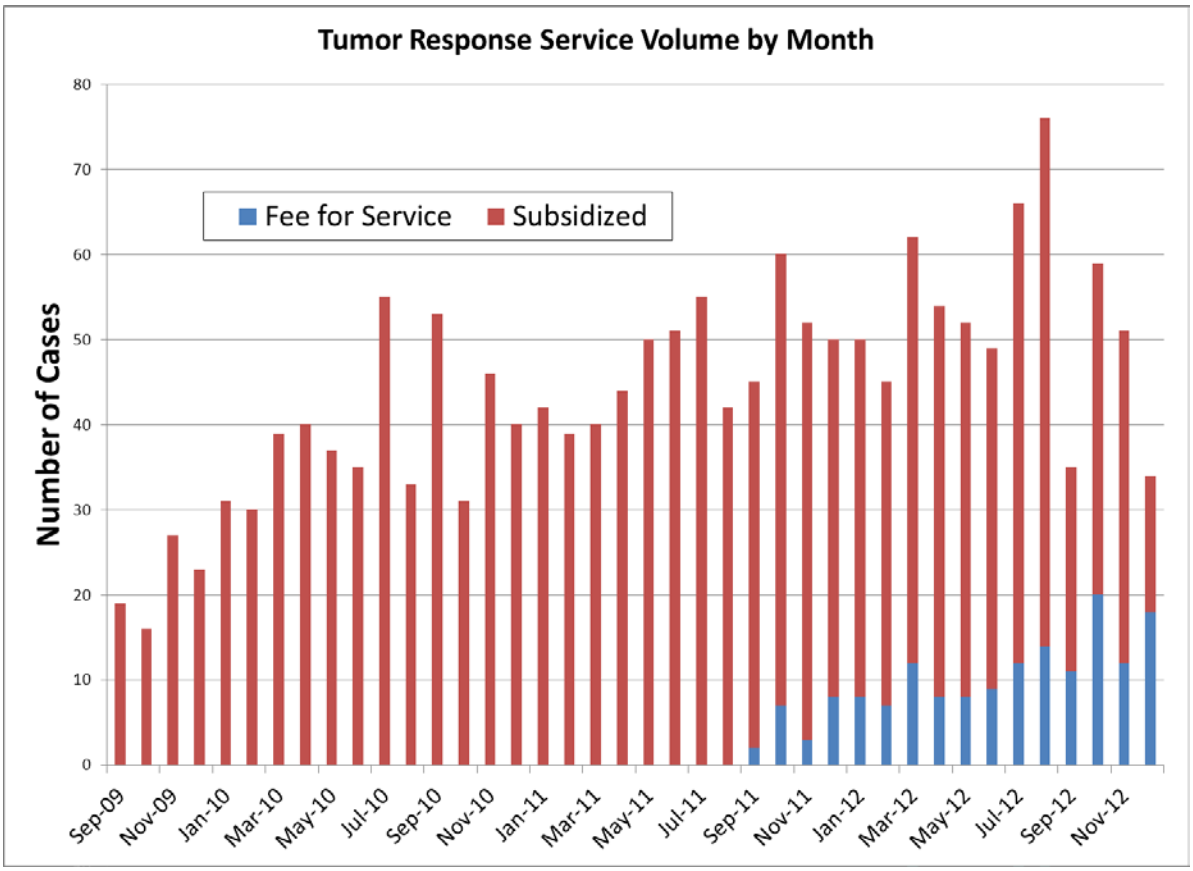
Tumor Measurement Tracking Source Document
TARGET LESIONS

STUDY :	UPCC 03909
Patient Name:	MM
Patient Study #	057
Measurement Criteria Used for this Study:	RECIST 1.0

DATE OF TEST:		1/3/2012		2/27/2012		5/3/2012	
METHOD OF EVALUATION:		CT		CT		CT	
TIMEPOINT OF TEST:		F/U 6		F/U 7		F/U 8	
		(cm)		(cm)		(cm)	
LESION #	SITE	MEASUREMENT	SERIES/ IMAGE	MEASUREMENT	SERIES/ IMAGE	MEASUREMENT	SERIES/ IMAGE
1	LIVER	4.6	4_36	4.5	4_31	4.9	8_34
2	LIVER	4.3	4_36	4.1	4_31	4.3	8_33
3	LIVER	5.3	4_56	5.5	4_53	5.5	8_53
4	PELVIS	8.2	4_100	8.6	4_98	9.3	8_97
5	PELVIS	3.8	4_104	4.4	4_105	4.2	8_103
6							
7							
8							
9							
10							
Sum		26.2		27.1		28.2	
		11%		14%		19%	
Response: (CR,PR,SD,PD)		SD		SD		SD	
Radiologist Signature:							
	Date:	1/17/2012		3/11/2012		5/19/2012	

In September of 2011, we initiated a fee-for-service system to stabilize the growth of the service requests, and to provide income for future expansion of the service. At that time, all clinical trials for which pre-existing tumor response services were performed were “grandfathered” into covered (subsidized) services, whereas new trial protocols were registered under the new fee-for-service system. Modest per-protocol, -patient, and -time point fees were introduced, with reduced rates for investigator-initiated and co-operative group trials.

At the time of this final report, the Tumor Response Service is processing image analysis requests at a rate of 40-60 cases per month. Over 1800 individual subject-time points have been registered in the system, with nearly 10000 quantitative and qualitative (i.e. non-target) tumor assessments performed. The usage tables over time for the Tumor Response Service are shown graphically below.



The graphic demonstrates steady growth in volume of the core over the initial two-year period. This was followed by a leveling off of volume after initiation of the fee-for-service model, and a slight decline in the latter months of the 2012 calendar year. This leveling off and decline is not unexpected, as the introduction of fee-for-service following a period of 100% subsidization led to a decline in new protocol registrations among some investigator-initiated studies. It should be noted, however, that the number of fee-for-service requests increased as a fraction of the total (averaging 34% of total over the last four months of 2012). We model continued growth in the number of fee-for-service studies for the next year, with an expected plateau of approximately 40 requests per month. Our modeling also indicates that the tumor response core is under-utilized by certain areas of the Cancer Center, including thoracic radiology and radiation oncology, allowing for additional avenues of outreach.

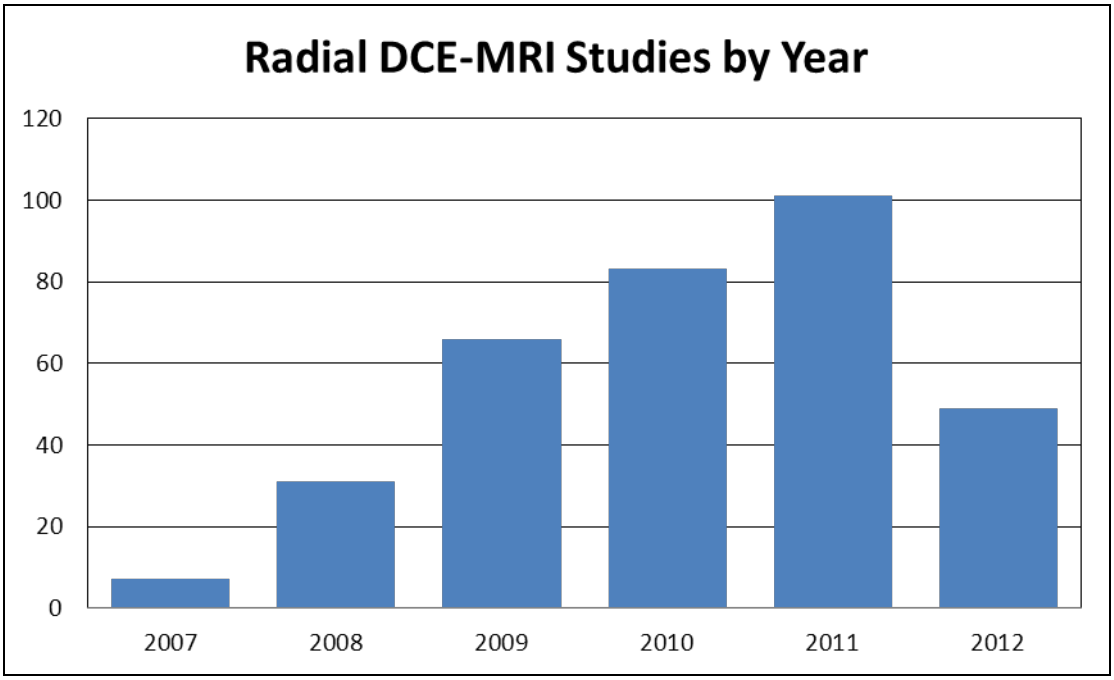
The continued success of the Tumor Response Service will provide data to justify the ongoing support of the CIC from the Department of Radiology and the ACC, through internal funding mechanisms as well as through the Cancer Center Support Grant.

C. <u>Development of broadened integration of novel imaging biomarkers for use in early-phase clinical trials in the ACC.</u>

Throughout the funding period, efforts have been underway to develop the Oncologic MRI

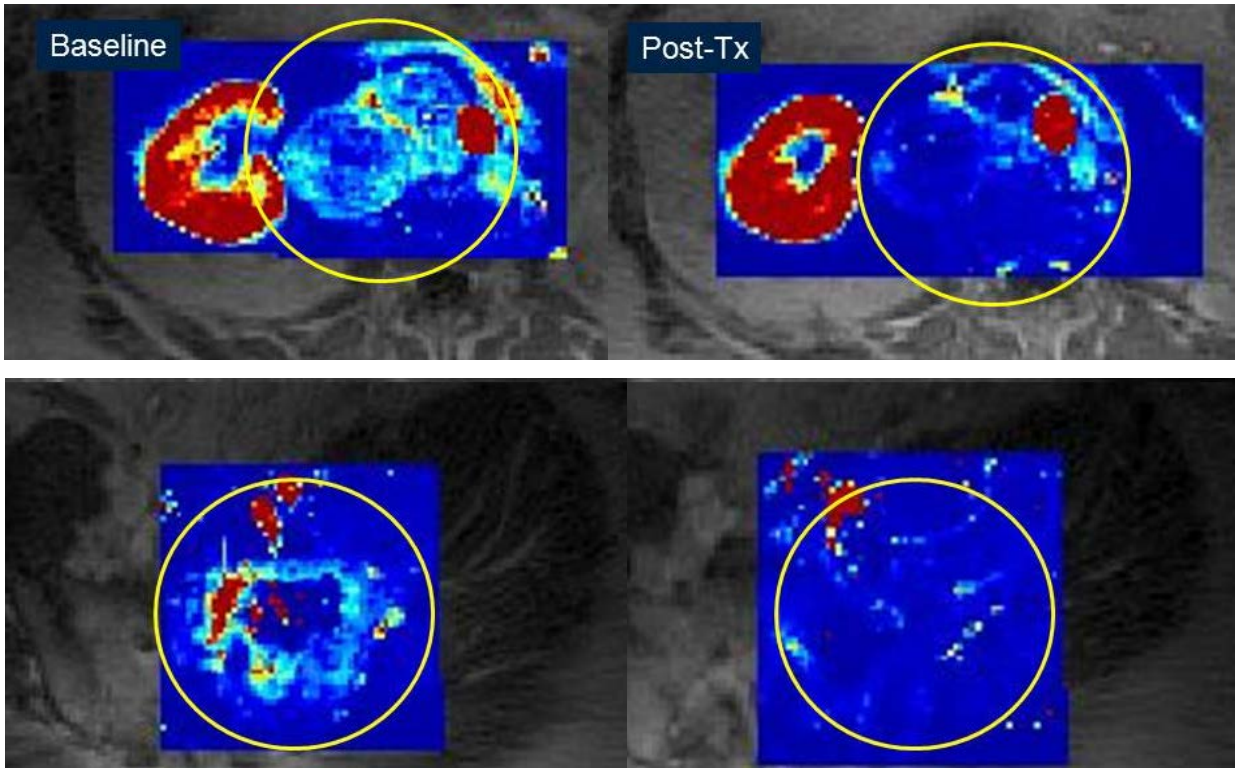
Response Laboratory as an example of novel imaging biomarkers to predict cancer outcomes. This work represents an extension of prior work by the project leader (Dr. Rosen), who—in conjunction with members of the Developmental Therapeutics Division of the Abramson Cancer Center—has provided leadership on the development of novel MRI biomarkers of cancer response. Work in this area initially focused on the use of DCE-MRI to determine early perfusion changes in tumors after administration of vascular targeted anti-cancer therapies. This prior work had demonstrated the ability of MRI to identify early changes in tumors treated with the vascular disruptive agent combretastatin A4 phosphate (Stevenson, 2003), or CA4P, and in renal cell tumors treated with sorafenib (Flaherty, 2008). In the latter case, pre-therapy assessment of tumor vascularity was shown to be predictive of long-term clinical response. In order to facilitate the incorporation of DCE-MRI into more routine clinical assessments of patients undergoing anti-vascular therapy, we determined that more robust large-volume dynamic enhanced imaging performed during free-breathing was required. This led to the a partnership with the laboratory of Hee Kwon Song, PhD, to adapt previous work in dynamic radial MRI imaging (Song, et al., 2004) to body MRI applications (Lin, 2008). We discovered that this type of imaging provided for fewer respiratory artifacts (Kim, 2008), and could be employed over large volumes using coronal plane imaging while maintaining adequate temporal resolution via KWIC image processing (Xue, 2012).

This work has yielded fruit in helping to develop robust DCE-MRI methodologies in early phase clinical trials. Our work has been adapted for use in various phase I and higher patient populations. Growth of the DCE-MRI service over the funding period is shown in the graphic below:

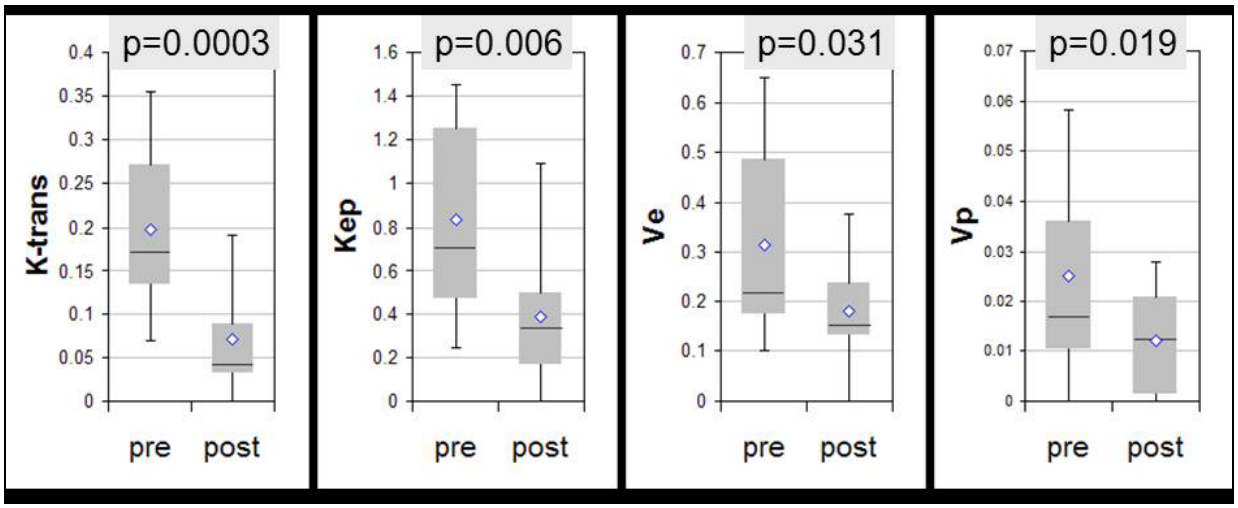


The growth in 2010-11 was spurred by a large scale trial of DCE-MRI in subjects with locally advanced NSCLC. Despite the drop in usage in 2012, we expect continued growth with the introduction of several new trials planned for 2013.

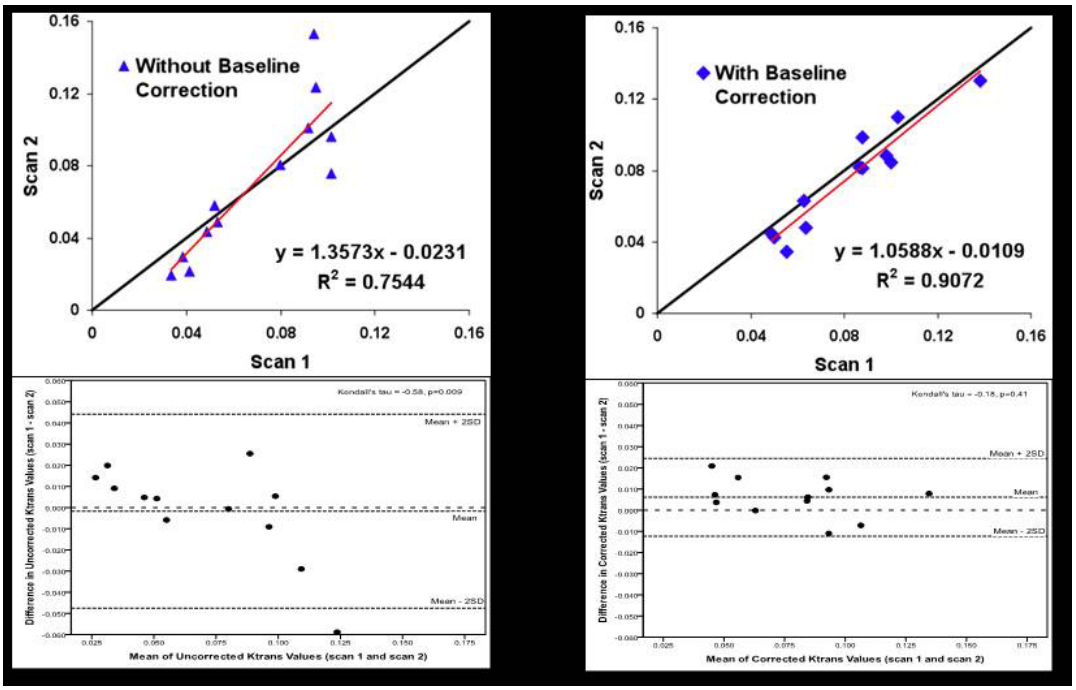
We have also developed improved modeling methods to provide pixel-wise DCE-MRI parametric images of tumors before and three weeks after the application of anti-vascular therapies. Two examples from our trial of sunitinib in renal cell carcinoma patients are shown below, detailing the marked decrease in tumor perfusion after several weeks of therapy, and well before any substantial change in tumor size:



Furthermore, with the advantage of higher temporal resolution from KWIC processing of DCE-MRI data, we have been able to show that renal cell tumors undergo changes in both blood volume and vascular permeability in the early post treatment period (see below). These results provide an additional potential prognostic and/or predictive biomarker for RCC patients undergoing anti-vascular therapies.



In addition, we have begun to refine our quantitative modeling methods to improve the reproducibility of DCE-MRI. We used a cohort of subjects with locally advanced lung cancer who underwent replicate DCE-MRI testing on separate days prior to beginning combined chemo-radiotherapy. Through adjustment of the baseline (pre-gadolinium) image intensity to account for Rician noise inherent in magnitude images, we have achieved an approximately two-fold reduction in the co-efficient of variation of tumor K^{trans} through adjustment of the baseline (Xue, 2011).



Currently, new DCE-MRI projects in renal cell carcinoma, hepatocellular carcinoma, prostate cancer, and colon cancer are underway, as are explorations of DCE-MRI in assessing the

response of normal tissues to radiation therapy. Furthermore, we have incorporated diffusion weighted imaging (DWI) into the oncologic MRI protocols throughout the body, and are currently exploring avenues of merging multi-B value DWI (IVIM modeling) with DCE-MRI to more completely evaluate the effects of various standard and targeted chemotherapy agents on the tumor micro-environment.

REFERENCES CITED

Flaherty KT, Rosen MA, Heitjan DF, et al. Pilot study of DCE-MRI to predict progression-free survival with sorafenib therapy in renal cell carcinoma. Cancer Biol Ther 2008;7(4).

Kim, S., Dougherty, L., Rosen, M., A. Kwon Song, H., and Poptani, H. (2008) Automatic correction of in-plane bulk motion artifacts in self-navigated radial MRI, *Magnetic Resonance Imaging 26*, 367-378.

Lin W, Guo J, Rosen MA, et al: Respiratory motion-compensated radial dynamic contrast-enhanced (DCE)-MRI of chest and abdominal lesions. Magn Reson Med 60:1135-46, 2008.

Song HK, Dougherty L: Dynamic MRI with projection reconstruction and KWIC processing for simultaneous high spatial and temporal resolution. Magn Reson Med 52:815-24, 2004.

Stevenson JP, Rosen M, Sun W, Gallagher M, Haller DG, Vaughn D, Giantonio F, Zimmer R, Petros WP, Stratford M, Chaplin D, Young Sl, Schnall M, O'Dwyer PJ: Phase I trial of the antivascular agent combretastatin A4 phosphate on a five-day schedule to patients with cancer: magnetic resonance imaging evidence for altered tumor blood flow. J Clin Oncol 21(23): 4428-4438, 2003.

Xue Y, Yu J, Rosen MA, et al: Enhanced perfusion measurement accuracy in DCE-MRI via improved baseline signal estimation, Proc., ISMRM, 19th Scientific Meeting. Montreal, 2011, pp 1093.

Xue Y, Yu J, Kang HS, Englander S, Rosen MA, Song HK. Automatic coil selection for streak artifact reduction in radial MRI. Magn Reson Med 2012; 67:470-476.

18. Extent of Clinical Activities Initiated and Completed. Items 18(A) and 18(B) should be completed for all research projects. If the project was restricted to secondary analysis of clinical data or data analysis of clinical research, then responses to 18(A) and 18(B) should be "No."

18(A) Did you initiate a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

_____Yes
__X___No

18(B) Did you complete a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

_____Yes
___X__No

If "Yes" to either 18(A) or 18(B), items 18(C) – (F) must also be completed. (Do NOT complete 18(C-F) if 18(A) and 18(B) are both "No.")

18(C) How many hospital and health care professionals were involved in the research project?

_____Number of hospital and health care professionals involved in the research project

18(D) How many subjects were included in the study compared to targeted goals?

_____Number of subjects originally targeted to be included in the study
_____Number of subjects enrolled in the study

Note: Studies that fall dramatically short on recruitment are encouraged to provide the details of their recruitment efforts in Item 17, Progress in Achieving Research Goals, Objectives and Aims. For example, the number of eligible subjects approached, the number that refused to participate and the reasons for refusal. Without this information it is difficult to discern whether eligibility criteria were too restrictive or the study simply did not appeal to subjects.

18(E) How many subjects were enrolled in the study by gender, ethnicity and race?

Gender:
_____Males
_____Females
_____Unknown

Ethnicity:
_____Latinos or Hispanics
_____Not Latinos or Hispanics
_____Unknown

Race:
_____American Indian or Alaska Native
_____Asian
_____Blacks or African American
_____Native Hawaiian or Other Pacific Islander
_____White
_____Other, specify:_____
_____Unknown

18(F) Where was the research study conducted? (List the county where the research study was conducted. If the treatment, prevention and diagnostic tests were offered in more than one county, list all of the counties where the research study was conducted.)

19. Human Embryonic Stem Cell Research. Item 19(A) should be completed for all research projects. If the research project involved human embryonic stem cells, items 19(B) and 19(C) must also be completed.

19(A) Did this project involve, in any capacity, human embryonic stem cells?
_____Yes
___X__ No

19(B) Were these stem cell lines NIH-approved lines that were derived outside of Pennsylvania?
_____Yes
_____ No

19(C) Please describe how this project involved human embryonic stem cells:

20. Articles Submitted to Peer-Reviewed Publications.

20(A) Identify all publications that resulted from the research performed during the funding period and that have been submitted to peer-reviewed publications. Do not list journal abstracts or presentations at professional meetings; abstract and meeting presentations should be listed at the end of item 17. **Include only those publications that acknowledge the Pennsylvania Department of Health as a funding source** (as required in the grant agreement). List the title of the journal article, the authors, the name of the peer-reviewed publication, the month and year when it was submitted, and the status of publication (submitted for publication, accepted for publication or published.). Submit an electronic copy of each publication or paper submitted for publication, listed in the table, in a PDF version 5.0.5 (or greater) format, 1,200 dpi. Filenames for each publication should include the number of the research project, the last name of the PI, the number of the publication and an abbreviated research project title. For example, if you submit two publications for PI Smith for the "Cognition and MRI in Older Adults" research project (Project 1), and two publications for PI Zhang for the "Lung Cancer" research project (Project 3), the filenames should be:

Project 1 – Smith – Publication 1 – Cognition and MRI
Project 1 – Smith – Publication 2 – Cognition and MRI
Project 3 – Zhang – Publication 1 – Lung Cancer
Project 3 – Zhang – Publication 2 – Lung Cancer

If the publication is not available electronically, provide 5 paper copies of the publication.

Note: The grant agreement requires that recipients acknowledge the Pennsylvania Department of Health funding in all publications. Please ensure that all publications listed acknowledge the Department of Health funding. If a publication does not acknowledge the funding from the Commonwealth, do not list the publication.

Title of Journal Article:	Authors:	Name of Peer-reviewed Publication:	Month and Year Submitted:	Publication Status (check appropriate box below):
1. None				☐Submitted ☐Accepted ☐Published

20(B) Based on this project, are you planning to submit articles to peer-reviewed publications in the future?

Yes____X_____ No_____

If yes, please describe your plans:

Summary article describing the Tumor Response Services of the University of Pennsylvania, and comparison of adequacy of response assessments compared to those achieved via mining of routine clinical radiology reports.

21. Changes in Outcome, Impact and Effectiveness Attributable to the Research Project. Describe the outcome, impact, and effectiveness of the research project by summarizing its impact on the incidence of disease, death from disease, stage of disease at time of diagnosis, or other relevant measures of outcome, impact or effectiveness of the research project. If there were no changes, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

No direct impact of disease outcomes was derived from the supported research. The supported research indirectly affected the overall mission of the Abramson Cancer Center whose mission is to reduce the mortality and morbidity form cancer through innovative basic science and clinical trial work.

22. Major Discoveries, New Drugs, and New Approaches for Prevention Diagnosis and Treatment. Describe major discoveries, new drugs, and new approaches for prevention, diagnosis and treatment that are attributable to the completed research project. If there were no major discoveries, drugs or approaches, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

None

23. Inventions, Patents and Commercial Development Opportunities.

23(A) Were any inventions, which may be patentable or otherwise protectable under Title 35 of the United States Code, conceived or first actually reduced to practice in the performance of work under this health research grant? Yes_____ No____X_____

If "Yes" to 23(A), complete items a – g below for each invention. (Do NOT complete items a - g if 23(A) is "No.")

a. Title of Invention:

b. Name of Inventor(s):

c. Technical Description of Invention (describe nature, purpose, operation and physical, chemical, biological or electrical characteristics of the invention):

d. Was a patent filed for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No____

If yes, indicate date patent was filed:

e. Was a patent issued for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No____
If yes, indicate number of patent, title and date issued:
Patent number:
Title of patent:
Date issued:

f. Were any licenses granted for the patent obtained as a result of work performed under this health research grant? Yes_____ No____

If yes, how many licenses were granted?_____

g. Were any commercial development activities taken to develop the invention into a commercial product or service for manufacture or sale? Yes___ No____

If yes, describe the commercial development activities:

23(B) Based on the results of this project, are you planning to file for any licenses or patents, or undertake any commercial development opportunities in the future?

Yes_____ No____X_____

If yes, please describe your plans:

24. Key Investigator Qualifications. Briefly describe the education, research interests and experience and professional commitments of the Principal Investigator and all other key investigators. In place of narrative you may insert the NIH biosketch form here; however, please limit each biosketch to 1-2 pages. *For Nonformula grants only – include information for only those key investigators whose biosketches were not included in the original grant application.*

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2. Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Mark Rosen	POSITION TITLE Associate Professor of Medicine
eRA COMMONS USER NAME (credential, e.g., agency login) marosen	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Amherst College, Amherst, MA	BA	1982-86	Chemistry
Columbia University, New York, NY	PhD	1988-1992	Biochemistry
Columbia University, New York, NY	MD	1986-88; 1992-94	Medicine
Babies' & Children's Hospital, New York, NY	Internship	1994-95	Pediatrics
Thomas Jefferson Hospital, Philadelphia, PA	Residency	1995-99	Diagnostic Radiology
University Of Pennsylvania, Philadelphia, PA	Fellowship	1999-2001	Body MRI

A. Personal Statement

I am an abdominal/body MRI radiologist in the Department of Diagnostic Radiology at the University of Pennsylvania, with 12 years' experience in routine and advanced CT and MRI applications in cancer imaging. I have extensive experience in clinical trial work in oncologic imaging at the University of Pennsylvania and through the American College of Radiology Imaging Network (ACRIN). Since 2007, I have served as the medical director of the CT/MRI core laboratory at ACRIN, supervising image acquisition and analysis for RECIST analysis in phase III trials, as well as imaging endpoints using tumor volumetrics, MRS, and DCE-MRI. Since 2009, I have also served as the director of the Clinical Imaging Core, a shared resource of the Abramson Cancer Center at the University of Pennsylvania, specializing in all aspects of imaging support (logistics, regulatory, acquisition, and analysis) for oncology clinical trials at Penn.

B. Positions and Honors

Professional Experience

2001-2009 Assistant Professor, Department of Radiology, University of Pennsylvania, Philadelphia, PA
2009- Associate Professor, Department of Radiology, University of Pennsylvania, Philadelphia, PA

Other Positions (Selected)

2009- Director, Clinical Imaging Core, Abramson Cancer Center, University of Pennsylvania
2007- Medical Director, CT/MRI Core Laboratory, American College of Radiology Imaging Network
2012- Member, Biomedical Imaging Technology Study Section A, National Institute of Health
2008- Member, Perfusion, Diffusion Flow Committee, Quantitative Imaging Biomarker Alliance
2007- Member, Hepatobiliary Cancer Task Force, National Cancer Institute
2008-2012 Member, Steering Committee, American College of Radiology Imaging Network
2004-2012 Member, Abdominal Committee, American College of Radiology Imaging Network

C. Selected Peer-Reviewed Publications (since 2011)

1. Kang HC, Tan KS, Keefe SM, Heitjan DF, Siegelman ES, Flaherty KT, O'Dwyer PJ, **Rosen MA**. MRI assessment of early tumor response in metastatic renal cell carcinoma patients treated with sorafenib. AJR Am J Roentgenol 2013; 200:120-126.

2. Xue Y, Yu J, Kang HS, Englander S, **Rosen MA**, Song HK. Automatic coil selection for streak artifact reduction in radial MRI. Magn Reson Med 2012; 67:470-476.
3. Rengan R, Mick R, Pryma D, **Rosen MA**, Lin LL, Maity AM, Evans TL, Stevenson JP, Langer CJ, Kucharczuk J, Friedberg J, Prendergast S, Sharkoski T, Hahn SM. A phase I trial of the HIV protease inhibitor nelfinavir with concurrent chemoradiotherapy for unresectable stage IIIA/IIIB non-small cell lung cancer: a report of toxicities and clinical response. J Thorac Oncol 2012; 7:709-715. PMCID: PMC3310889.
4. Sun W, Sohal D, Haller DG, Mykulowycz K, **Rosen M**, Soulen MC, Caparro M, Teitelbaum UR, Giantonio B, O'Dwyer PJ, Shaked A, Reddy R, Olthoff K. Phase 2 trial of bevacizumab, capecitabine, and oxaliplatin in treatment of advanced hepatocellular carcinoma. Cancer 2011; 117:3187-3192.
5. Flaherty KT, Lathia C, Frye RF, Schuchter L, Redlinger M, **Rosen M**, O'Dwyer PJ. Interaction of sorafenib and cytochrome P450 isoenzymes in patients with advanced melanoma: a phase I/II pharmacokinetic interaction study. Cancer Chemother Pharmacol 2011; 68:1111-1118.

D. Research Support

ACTIVE:

1. P30-CA016520-36 Rev (PI: Dang) 7/13/2011-11/30/2015
NIH Role: Resource Director
Abramson Cancer Center Core Support Grant
This grant supports the cancer research effort of the Abramson Cancer Center of the University of Pennsylvania.
2. 2U01-DK062494-10 (PI: Olthoff) 9/30/2009-8/31/2014
NIH Role: Co-Investigator
Adult to Adult Living Donor Liver Transplantation Cohort Study
This grant supports the evaluation of liver transplantation efficacy across multiple liver transplantation centers.
3. R01-CA136535-03 (PI: Feldman) 7/17/2009-6/30/2014
NIH Role: Co-Investigator
Software to facilitate multimode, multiscale fused data for Pathology & Radiology
This grant seeks to develop and evaluate multi-modal image analysis for fused imaging and pathology datasets.
4. ACRIN MR/CT Core Lab (PI: Rosen) 1/1/2006-12/31/2013
ACRIN Role: Principal Investigator
ACR Imaging Network MR/CT Core Lab
Agreement for Dr. Rosen to serve as the medical director for the American College of Radiology Imaging Network CT/MR Core Lab.
5. V Foundation (PI: Rosen) 11/1/2010-10/30/2013
V Fndn. for Cancer Research Role: Principal Investigator
Use of PET and MR Imaging Biomarkers to Predict Response of RCC to Tyrosine Kinase Inhibitor Therapy
This grant evaluates MRI and PET methods to determine the biology of RCC tumors and their response to treatment.
6. R01-CA139003-02 (PI: O'Dwyer) 8/3/2009-6/30/2013
NIH Role: Co-Investigator
Modulation of the Interaction of Anti-Angiogenic and Cytotoxic Therapies in Colorectal Cancer
This grant seeks to optimize combination targeted and cytotoxic therapy in colorectal cancers.