

# **American College of Radiology**

## **Annual Progress Report: 2006 Formula Grant**

### **Reporting Period**

July 1, 2009 – June 30, 2010

### **Formula Grant Overview**

The American College of Radiology received \$2,511,654 in formula funds for the grant award period January 1, 2007 through December 31, 2010. Accomplishments for the reporting period are described below.

### **Research Project 1: Project Title and Purpose**

*Factors Associated with Attrition in RTOG Clinical Trials* - To date, many studies have examined barriers to clinical trial recruitment; however, we know substantially less about retention of subjects enrolled in randomized controlled trials (RCT). Indeed, only one out of four subjects remains in RCT until study completion. Therefore, there is a compelling need to study retention in order to design strategies to enhance retention in Radiation Therapy Oncology Trials (RTOG). The purpose of the proposed project is to assess individual (e.g., socio-demographics of age, gender, race/ethnicity), organizational (e.g., community versus academic setting), and protocol-related factors (e.g., phase of trial, group assignment, adverse events) associated with attrition in all RTOG treatment studies that were opened to accrual as of January 1, 1985 and have completed accrual and had the primary endpoint published by January 1, 2005.

### **Duration of Project**

7/1/2007 – 6/30/2009

### **Summary of Research Completed**

This project ended during a prior state fiscal year. For additional information, please refer to the Commonwealth Universal Research Enhancement C.U.R.E. Annual Reports on the Department's Tobacco Settlement/Act 77 web page at <http://www.health.state.pa.us/cure>.”

### **Research Project 2: Project Title and Purpose**

*Identifying Interventions for Cancer Patients at High Risk for Poor Outcomes* - In this two phase project, the first goal is to document the combined influence of gender, marital/partner status, and race in identifying patients with cancer at risk for poor outcomes in a pooled analysis of patients with cancers treated with radiotherapy on large, national clinical trials. This analysis will facilitate understanding how the interaction of these factors influences intermediate indicators [e.g., treatment breaks, weight loss, etc.] of primary outcomes [e.g., survival, quality

of life]. The second goal is to use these results in designing a second phase of focus group discussions aimed at developing targeted interventions to improve both the intermediate indicators and, ultimately, survival and quality of life.

### **Anticipated Duration of Project**

7/1/2007 - 12/31/2010

### **Project Overview**

Objective: The classic prognostic factors in clinical oncology trials remain clinical stage and performance status. Recently, a striking disadvantage in cancer outcomes has been observed for single males. This work leads to the hypothesis that the interaction among gender, partner status, and race delineates a group at particular risk for poor outcomes, namely unpartnered African American males. The broad objective is to identify targeted interventions to ameliorate the effects of factors that place this population at risk.

Specific aims: To investigate disparities in health outcomes among specific populations prevalent in the Commonwealth by assessing differential primary outcomes [e.g., survival and quality of life] and secondary intermediate outcomes [e.g., treatment breaks, weight loss, etc] by key sociodemographic factors [gender, marital/partner status, race] in a meta-analysis of patients treated for cancer on national clinical trials. This information will be used to guide focus group discussions identifying factors amenable to targeted interventions to improve intermediate outcomes. The project thus progresses from clinical epidemiological findings to interventions development, addressing health disparities concentrated among African American males, particularly those without partners.

Design and methods: A two phase, quantitative-qualitative design: Phase 1: A pooled analysis of prospective data for colorectal, head & neck, lung and prostate cancer clinical trials will be conducted using statistical methods to identify interactions among key sociodemographic factors [gender, marital/partner status, race] that, when combined, may lead to poorer outcomes than would be expected based upon standard prognosticators alone. After the populations at highest risk are identified, the next step will be to explore how the interaction of these factors influences intermediate indicators [e.g. treatment breaks, weight loss, etc] of primary outcomes [e.g., survival, quality of life]. In Phase 2, results of Phase 1 will determine purposive sampling and interview guides for focus groups. The objective of these focus group discussions will be to determine how disparities emerge in the process of care and how timely and targeted interventions could improve outcomes in the high-risk population.

Candidates for intervention include deficits in self-care, such as nutrition and receipt of prompt medical care for treatment side effects and symptom distress that otherwise interfere with treatment adherence.

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### **Expected Research Outcomes and Benefits**

The outcomes of this project will be a clearer understanding of specific populations at high risk for poor outcomes after state of the art cancer therapies and the concrete means by which disparities in outcomes can be remedied. The identification of African American single males as a particularly high risk could have important clinical and policy implications. Moreover, the two phase strategy provides a means of using qualitative focus group discussions to translate recognition of quantitative factors directly into cost-effective interventions to facilitate intermediate factors [such as scheduled doctor visits, treatment breaks, weight loss, or medication compliance] that impact on primary outcomes [such as survival, toxicity, and quality of life] among those patients at highest risk. Such intermediate factors present opportunities for prompt intervention forestalling negative outcomes, including failure to derive the full potential benefit of treatment.

The proposed project is novel in specifying a way in which more precise delineation of health disparities can be translated directly into appropriate interventions and improved outcomes. The benefits of this study are that the findings will lead to targeted interventions to improve these intermediate factors that have a cascade effect on primary outcomes, such as quality of life and survival. Specifically, once the cancer patient populations are identified [by gender, marital/partner status, race, or specific combinations of these factors] at highest risk for poor outcomes, this will facilitate testing of methods of early identification and social support interventions to directly improve cancer outcomes. These interventions will be based upon the focus group recommendations composed of the high-risk cancer patient populations. This project will thereby address disparities in health status that affect many Commonwealth populations.

### **Summary of Research Completed**

Phase 1: Meta-analysis of prospective data for patients treated for cancer on national clinical trials

The third analysis of this grant focused on the “Impact of Marital Status and Race on Outcomes of Patients Enrolled in Radiation Therapy Oncology Group Prostate Cancer Trials”. In this report we examine the effect of race and marital status on outcomes in men treated with radiation therapy for prostate cancer. We hypothesize that the interaction among the key sociodemographic factors of marital status and race will assist in the identification of critical predictors for poor outcomes for prostate cancer patients. This report is a meta-analysis of patients with prostate cancer treated in three prospective RTOG clinical trials, RTOG 9202, 9406, and 9413.

### Statistical Methods

An event affecting overall survival (OS) was defined as death due to any cause, and time to death was measured from date of randomization to date of death or the last clinical follow-up. Biochemical failure (BF) was defined as a > 2 ng/ml rise in PSA above the PSA nadir, after the end of radiation therapy or after the end of salvage therapy. An event affecting disease-free survival (DFS) was defined as one of the following: death due to any cause, local failure, biochemical failure (as defined above), distant metastases, or second primary.

The Kaplan-Meier method was used to estimate the survival rate for OS and DFS and the cumulative incidence method was used for failure rate for BF. To analyze whether each covariate was independently associated with outcomes while adjusting for other covariates, the Cox proportional hazards regression models were used for OS and DFS and Fine and Gray’s regression models were used for BF. Unadjusted and adjusted hazard ratios (HR) were calculated for all covariates using either the Cox or Fine and Gray’s proportional hazards model or a logistic regression model with associated 95% confidence intervals (C.I.) and p-values. All statistical tests were two-sided and a p-value <0.05 was considered to be statistically significant. Statistical Analysis System (SAS Institute, Cary, NC) and R software was used for all statistical analyses.

### Results

A total of 3,570 patients with complete covariate information from 3 RTOG prostate cancer trials were examined in this meta-analysis. Of these, 1,358 patients were enrolled on RTOG 9202, 999 patients were enrolled on RTOG 9406, and 1,213 patients were enrolled on RTOG 9413. At the time of analysis, 1,381 (39%) of these patients had died (OS), 2,547 (71%) had experienced disease recurrence or died (DFS), and 1,537 (43%) had experienced biochemical failure (BF). The median follow up was 7.22 years for all patients, and 7.95 years for the surviving patients. To account for changes in accepted treatment for prostate cancer over time, all analyzable patients were stratified for accrual years: 1992-1994, 1995-1997, and 1998-2000. The major covariates of race and marital status were considered in all outcomes. Other covariates were considered for each outcome in addition to the race and marital status. These covariates were age, clinical stage, Karnofsky Performance Score (KPS), Gleason Score, Prostate Specific Antigen (PSA), Biologic Effective Dose (BED), and type of treatment received. The median age was 70 years old (range 41-88) with 53% of the patients ≤ 70 years old and 47% of the patients > 70 years old. 2,741 (77%) of the patients were white and 829 (23%) of the patients were non-white. Of the non-white patients, 78% were Black, 15% were Hispanic, 3% were Asian, 2% were Native American, and 2% were Other. Of the patients, 76% were married and 24% were single. The performance status in this group was generally excellent, with 94% of the patients with KPS

90-100. There was a notable difference between patients stratified across accrual years in that, in later accrual years, more people were in the PSA <10 category and had a lower T and N staging, as well as being treated to a higher BED of radiation.

Heterogeneity testing was next performed in order to determine if a pooled estimate could be used to represent the combined data from the trials in this meta-analysis. This demonstrated that the stratification groups were homogeneous in respect to their adjusted hazard ratios, and the pooled adjusted hazard ratio was noted for each outcome. We therefore proceeded to use pooled hazard ratios for our analysis.

In our patient population, there was a statistically significant overall survival benefit in married men with prostate cancer, with the HR for single status compared to married status being 1.36 (95% CI, 1.2 to 1.53). There was no significant overall survival difference between white patients and non-white patients, with a HR for non-white compared to white patients of 1.05 (CI 0.92 to 1.21). In contrast, the DFS HR and BF HR were both not significantly different between single and married patients, HR 1.05 (95% CI 0.96 to 1.16) and 0.92 (95% CI 0.82 to 1.05), respectively. Similarly, the DFS HR and BF HR were also not significantly different between white patients and non-white patients, 0.92 (95% CI 0.83 to 1.01) and 0.87 (95% CI 0.77 to 0.99), respectively.

Subgroup analysis of marital status and race was performed. Five-year survival and event estimates were calculated for OS, DFS, and BF, in single white, single non-white, married white, and married non-white patients. For OS, single white and single non-white patients are at significantly higher risk of death from any cause than married white patients, HR 1.35 (95% CI 1.17 to 1.56) and HR 1.44 (95% CI 1.18 to 1.75). For DFS, single white patients are at significantly higher risk of recurrence than married white patients, with HR 1.17 (95% CI 1.05 to 1.30). All groups are at equal risk for biochemical failure at 5 years.

Further pairwise comparison of subgroups of marital status and race was performed. When compared to single white patients, single non-white patients had a decreased risk of DFS and BF, with DFS HR 0.77 (95% CI 0.64 to 0.92) and BF HR 0.75 (95% CI 0.59 to 0.96). However, despite these trends, there was no statistically significant difference in OS between the two groups. Married non-white and white patients, when compared to single white patients, had improved OS with HR 0.71 (95% CI 0.58 to 0.88) and 0.74 (95% CI 0.64 to 0.86), respectively, as well as improved DFS with HR 0.85 (95% CI 0.73 to 0.99) and 0.87 (95% CI 0.78 to 0.97), respectively, however no statistically significant difference was observed. Married non-white patients had no statistically significant difference in OS, DFS, and BF when compared to married white patients. Single non-white patients had worse OS, with OS HR 1.45 (95% CI 1.18 to 1.78), when compared to married white patients. This is despite no significant difference in DFS HR and an apparently decreased risk of BF with a HR of 0.76 (95% CI 0.62 to 0.94). Finally, married non-white patients had improved OS when compared to single non-white patients, with an OS HR of 0.69 (95% CI 0.54 to 0.88), again with no statistical difference.

Kaplan-Meier analysis of OS, DFS and BF for married compared to single patients was demonstrated. Median time to death (OS) for married men was 5.68 years and for single men was 4.73 years. Median time for DFS for married men was 7.25 years and for single men was

6.56 years. Median time for BF for married men was 7.81 years and for single men was 7.05 years. The median age of death for married men was 72 years old, and for single men was 70 years old.

In order to more carefully examine if there was an association between established prognostic factors and marital status, the variables of PSA, Gleason Score, KPS and T-stage were compared between married and single patients. While Gleason Score, KPS and T-stage were not significantly different between married and single patients, there was a significant difference in PSA levels between married and single patients. Of note, 45% of single patients and 40% of married patients presented with PSA > 20 and 28% of single patients and 33% of married patients presented with PSA < 10. This may be related to single men lacking the social support to seek early detection and treatment of prostate cancer. Further, single men were still at higher risk for worse survival when this initial PSA difference was taken into account.

### Conclusion

The analysis presented here identifies a subgroup of prostate cancer patients, defined by the sociodemographic factor of being single, who are at higher risk of mortality. This finding adds to the understanding of how sociodemographic factors, and their complex associations with economic, psychological, social, and biologic determinants, affect the outcome of cancer care. Whether strategies could be developed that would allow single patients to obtain the benefits of being married remains to be determined, however simple targeted clinical interventions appear to be feasible and should be implemented in prospective analyses that examines the clinical and biologic implications of such therapies.

### Publications

One manuscript has been published (reference below) and the manuscript for the prostate cancer study presented above is under review.

Siddiqui, F., Bae, K., Langer, C., Coyne, J., Gamerman, V., Komaki, R., Choy, H., Curran, W., Watkins-Bruner, D., Movsas, B. (2010). The Influence of Gender, Race, and Marital Status on Survival in Lung Cancer Patients: Analysis of Radiation Therapy Oncology Group Trials, *Journal of Thoracic Oncology*, 5(5):631-9. PMID: 20432520

### Focus Groups

The audio recordings of the focus groups have been transcribed and all transcriptions have been de-identified. The partnered group taking place on 6-17-2009 transcribed to 27 pages of content and the single group taking place on 6-26-2009 transcribed to 29 pages of content.

Due to several staffing changes, coding and data analysis of these transcriptions is still in progress.

### **Research Project 3: Project Title and Purpose**

*Translational Studies on Eliciting Effective Immune Responses to Pancreatic Carcinoma* - The development of multiple forms of cancer including pancreatic carcinoma may be prevented by maintaining effective immune surveillance mechanisms or by eliciting immune responses to tumor cells with therapeutic intent. Two molecules which are produced by pancreatic tumor cell and induce ineffective anti-tumor immune responses have been identified; these are interleukin-10 (IL-10) and transforming growth factor- $\beta$  (TGF- $\beta$ ). This project explores new strategies to block inappropriate production of IL-10 and TGF- $\beta$ . These studies originally focused on using drugs (EGFR/ErbB2 and STAT3 antagonists), which are already either in preclinical or clinical studies in various tumor forms including pancreatic carcinoma. Due to negative results obtained in the course of this work we have refocused our efforts on the development of more effective ways to enable immunologically-mediated, antibody-directed tumor cell destruction using engineered anti-EGFR antibodies.

### **Anticipated Duration of Project**

7/1/2007 - 12/31/2010

### **Project Overview**

Previous work has implicated aberrant activation of the epidermal growth factor receptor (EGFR) and the related ErbB2 receptor in progression of pancreatic cancer. Similarly, deregulated STAT3 signaling has previously been described in this tumor form. In addition, EGFR/ErbB2 signaling has been found to contribute to STAT3 activation in pancreatic cancer cell lines. These molecular aberrations have primarily been viewed as mechanisms by which pancreatic cancer cells achieve apoptosis resistance and acquire growth potential.

However, recent work in T cell lymphomas has highlighted a novel role of STAT3 activation in regulating the production of immunomodulatory cytokines by tumor cells, specifically, TGF- $\beta$  and IL-10. In preliminary work the principal investigator (PI) of this project demonstrated aberrant production of TGF- $\beta$  and IL-10 by pancreatic tumor cells *in vitro* and in patients. Furthermore, these tumor-derived cytokines appear to skew the immune response in pancreatic cancer patients to respond ineffectively to the tumor challenge. Specifically, the PI demonstrated previously that tumor-derived TGF- $\beta$  and IL-10 induce a DC2/Th2 immune phenotype.

Collectively, these findings raised several important questions: (1) Does aberrant STAT3 activation in pancreatic cancer cells contribute to IL-10/TGF- $\beta$  production? (2) What is the role of EGFR/ErbB2 signaling in STAT3 activation in pancreatic carcinoma? (3) Can EGFR/ErbB2/STAT3 blockade be used to reset ineffective immune responses to pancreatic tumor cells?

We determined that the EGFR/ErbB2/STAT3 signaling axis does not significantly contribute to production of IL-10 and/or TGF- $\beta$ , at least not in a panel of pancreatic carcinoma cell lines cultured *in vitro*. Thus, having refuted the main hypothesis of our original application and as outlined in detail in the last progress report we switched our focus towards developing EGFR

antagonistic antibody derivatives with improved therapeutic efficacy. This was within the purview of translational studies to elicit effective immune mechanisms with anti-tumor properties. Specifically, we set out to test a novel concept to molecularly ‘mask’ clinically proven monoclonal antibodies recognizing the EGFR such that they preferentially recognize antigen at disease (tumor) sites but not in normal tissues. This would lead to a very favorable therapeutic index of these agents compared to monoclonal antibodies currently in use in tumor therapy. As outlined above the EGFR is a molecular target frequently expressed or overexpressed in pancreatic carcinoma.

### **Principal Investigator**

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### **Expected Research Outcomes and Benefits**

Pancreatic cancer constitutes a deadly tumor form which, at the time of diagnosis, is largely refractory to conventional treatments. As in many epithelial cancers the EGFR has been implicated in the pathogenesis of pancreatic cancer and EGFR inhibitors have been used in the clinical management of pancreatic cancer. However, the use of EGFR inhibitors in the clinic is limited by adverse side effects, primarily affecting the skin and the gastrointestinal system. This circumstance prompted us to develop a new concept to target EGFR antagonistic antibodies to disease sites while avoiding binding to normal tissues under homeostatic conditions. Proving this concept has the potential to not only design better EGFR antagonistic antibodies but to improve a host of other monoclonal antibodies currently in clinical use as well.

### **Summary of Research Completed**

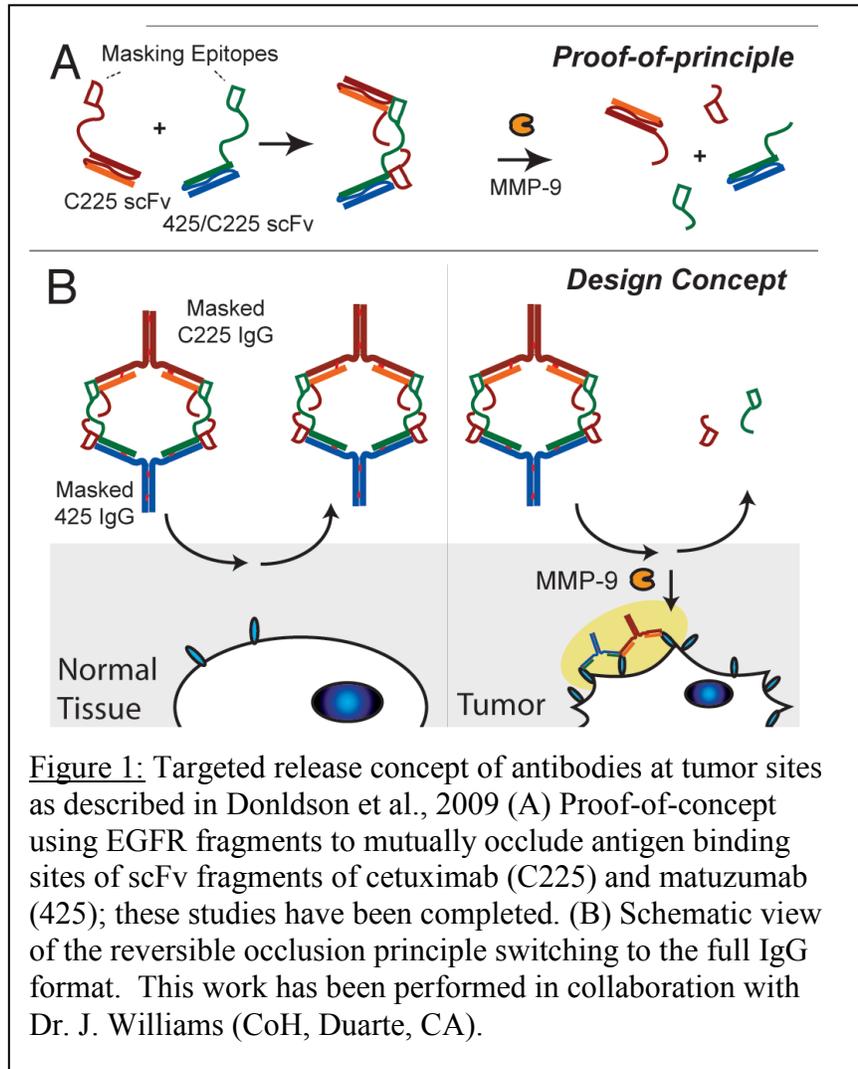
In our previous progress reports we presented results that did not support the original hypothesis that IL-10 secretion by pancreatic carcinoma cells (BxPC3, Capan-2, Sv8686) is affected by EGFR-dependent STAT3 activation. Similar results were obtained using human A431 cells which have very high EGFR expression levels and attendant STAT3 activation as published by us previously (Quadros et al., *Cancer Research* 64:3934-3939, 2004). Collectively these experiments suggest that the extent to which STAT3 activation affects IL-10 production may be tissue- or cell-type specific. Whereas this type of regulation is prevalent in immune cells it appears to be less prevalent in epithelial cells as used in the present study. Implicitly, EGFR blockade may not favorably affect the balance of immunoregulatory cytokines elaborated by tumor cells in the tumor microenvironment. Interestingly, we also observed that inhibition of src

kinase activity using the small molecule agent PP1 led to increased IL-10 secretion by A431 cells not decreased IL-10 production. These results do not support further exploration of immunomodulatory effects by EGFR blockade that could be exploited for immunotherapeutic approaches to pancreatic cancer.

Based on this result and, as also outlined above and described previously, we switched the main focus of our efforts to the development of EGFR inhibitors which are targeted specifically to tumor sites. This strategy is expected to markedly reduce the rate of adverse events associated with the use of these agents and contribute to the efficacy of EGFR inhibition in pancreatic cancer among different tumor types.

To this end we have produced recombinant versions of antibodies in which the antigen recognition sites (complementarity determining regions (CDRs)) are occluded by engineered antigen fragments. However, these fragments can be removed through proteolytic cleavage by tumor-associated proteases followed by engagement of native antigen in tumor tissues. In the last progress report we introduced this principle using two different monoclonal antibodies recognizing the EGFR (cetuximab and 425/matuzumab). The experiments in support of this concept have been completed and formed the basis for a scientific report published within this funding period (Donaldson et al., *Cancer Biol Ther* 8:2147-52, 2009 (PMID: 19783899)). Of note, this work has been done in close collaboration with Dr. J. C. Williams of City of Hope, Duarte, CA (formerly at the Dept. of Biochemistry, Thomas Jefferson University). Additional funding was obtained from intramural sources at Thomas Jefferson University and in the form of fellowship support for Dr. J. Donaldson who performed much of the work as part of his Ph.D. thesis. Specifically, it was shown by several biophysical and biological assay systems (surface plasmon resonance analysis, analytical ultracentrifugation, size exclusion gel electrophoresis, fluorescence-activated cell sorting analysis) that a complex of the two antibodies poorly recognized antigen. In contrast and as expected, cleavage of the constituent parts of the complex led to dissociation and antigen recognition on tumor target cells. These results provided proof-of-principle evidence that the concept is feasible and prepared the ground for further testing in a biologically meaningful in vivo test system as described in the next paragraph. It has also led to securing additional funds for this project from the National Institutes of Health (NCI) in the form of an R21 grant in which Dr. Rodeck and Dr. J. Williams serve as co-principal investigators. This small grant supplements the current funding through the ACR to propel the next phase of preclinical testing of the tumor-targeting concept using a combination of cetuximab and matuzumab.

Collectively, these results represent a significant conceptual step forward in antibody engineering to enable targeted release of biologics at disease sites. This technology has multiple applications in the immunotherapy of malignant tumors



**Figure 1:** Targeted release concept of antibodies at tumor sites as described in Donldson et al., 2009 (A) Proof-of-concept using EGFR fragments to mutually occlude antigen binding sites of scFv fragments of cetuximab (C225) and matuzumab (425); these studies have been completed. (B) Schematic view of the reversible occlusion principle switching to the full IgG format. This work has been performed in collaboration with Dr. J. Williams (CoH, Duarte, CA).

#### **Research Project 4: Project Title and Purpose**

*Correlating Tumor Markers/Genes with Clinical Outcome* - The vast RTOG clinical trials database offers extensive opportunities to explore associations between correlative data, such as tumor marker analysis, and patient outcome data. The purpose of this project is to perform translational research analyses that are not specified in the clinical trial protocol. The project will correlate translational data with clinical outcome and interpret the results for RTOG-run protocols for patients with brain tumors, sarcoma, pancreatic cancer, cervical cancer and head & neck cancer.

#### **Anticipated Duration of Project**

7/2007 - 12/31/2010

## **Project Overview**

The broad objectives of this research proposal are to (i) generate hypotheses that may lead to more efficient clinical trials and more patient-targeted treatments, and (ii) to add to the literature regarding correlations between tumor markers/genes and clinical outcomes. Specifically, clinical outcomes such as survival and disease progression will be correlated with the presence or absence of specific tumor markers/genes for patients treated for brain tumors, sarcoma, pancreatic cancer, cervical cancer, and head & neck cancer. Separate funding from several sources has been awarded to RTOG investigators to do tumor marker/gene biologic analyses in the aforementioned disease sites. After the tissue is analyzed, the resulting data is sent to and stored at RTOG headquarters in Philadelphia. The clinical trials have all completed patient accrual and their protocol specified primary endpoints reported. For this project, the marker/gene data will be combined with the clinical outcome data, analyzed and reported.

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## **Expected Research Outcomes and Benefits**

The identification of specific tumor markers/genes associated with better or worse outcome for cancer patients may allow future researchers to generate new hypotheses that may potentially lead to more efficient clinical trials that assign patient treatment based on the patient's tumor marker/genetic profile. In addition to aiding in the conduct of clinical trials, this type of research may help to tailor treatments to individual patients based on their genetic make-up. The combination of tumor marker data with RTOG's clinical outcome database is an extensive source for exploring these possible associations.

## **Summary of Research Completed**

**Aim:** Clinical outcomes such as survival and disease progression will be correlated with the presence or absence of specific tumor markers/genes for patients treated for brain tumors, sarcoma, pancreatic cancer, cervical cancer, and head & neck cancer.

During this past grant period two analyses were completed.

The first evaluated the effect of HPV status, as measured by p16, and tobacco pack-years on both overall survival (OS) and progression-free survival (PFS) for patients with oropharyngeal cancer

treated with radiation therapy on RTOG 9003 “A Phase III Randomized Study to Compare Twice Daily Hyperfractionation, Accelerated Hyperfractionation with a Split and Accelerated Fractionation with Concomitant Boost, to Standard Fractionation Radiotherapy for Squamous Cell Carcinomas of the Head and Neck”. Previous work showed that oropharyngeal cancer patients, treated with chemoradiation that were human papilloma virus (HPV) positive, had significantly higher OS and PFS than those patients that were HPV negative. This analysis evaluated the effect of HPV status for patients treated with radiation therapy alone, as well as evaluating the impact of tobacco pack-years. With a median follow-up of 9.3 years, oropharyngeal cancer patients that were HPV positive had better OS (5-year 49.0 vs. 19.6%,  $p<0.0001$ ; HR 0.43, 95%CI 0.31-0.61) and PFS (5-year 43.6 vs. 19.0%,  $p<0.001$ ; HR 0.45, 95%CI 0.32-0.63) than HPV negative patients. Local-regional failure was also significantly lower for HPV positive patients (5-year 30.5 vs. 54.9%,  $p<0.001$ ); however distant metastases (11.1 vs. 13.0%,  $p=0.71$ ) and second primary tumors (SPT, 13.8 vs. 11.4%,  $p=0.40$ ) were not. Additionally, the hazard for both the OS and PFS endpoints increased by 1% per tobacco pack year of smoking ( $p<0.002$ ), after adjusting for Zubrod status, tumor stage, nodal stage, and HPV status. Based on the significantly higher OS and PFS for HPV positive patients, it was decided that these populations should be separated for purposes of clinical trials. These results, in conjunction with HPV analyses of patients receiving chemoradiation, have led to a developing RTOG Phase III trial concept for HPV positive patients that are currently under review by the NCI and will use tobacco pack-years as a stratification variable.

These results were presented at the ASCO 2010 annual meeting and the manuscript is in progress.

The second analysis evaluated the correlations between each of Cytoplasmic E-cad, nuclear B-cat and nuclear Gli1 and the following efficacy endpoints: time to metastasis (TTM), time to progression (TTP), and overall survival (OS), as well as previously determined EGFR expression, for patients enrolled in RTOG 9003 “A Phase III Randomized Study to Compare Twice Daily Hyperfractionation, Accelerated Hyperfractionation with a Split and Accelerated Fractionation with Concomitant Boost, to Standard Fractionation Radiotherapy for Squamous Cell Carcinomas of the Head and Neck”. E-cad, B-cat, and Gli1 were also significantly correlated with each other, but none were correlated with EGFR expression. Gli1 was significantly associated with poorer TTM, TDP, and OS both on univariate and multivariate analyses; however, neither E-cad nor B-cat was correlated with the efficacy outcomes. Based on these results Gli1 may be an important prognostic factor for patients with head and neck cancer; however, independent validation of these results will be needed before this can be incorporated as a stratification factor and/or be used to define a patient population for a clinical trial.

These results were presented at the ASCO 2010 annual meeting and the manuscript is in progress.

## **Research Project 5: Project Title and Purpose**

*Emerging Imaging Technology Clinical Trials in PA* - This project represents the continued development of a clinical trials research network (developed under the 2004 C.U.R.E. formula funding) which will perform early stage imaging studies at selected Pennsylvania academic medical centers to advance the role of imaging in the detection and/or treatment of disease. Participants of the network will conduct a clinical trial to evaluate the role of Positron Emission Tomography (PET) and the classification ability of two novel imaging compounds to distinguish Alzheimer's disease from cognitively normal subjects. The conduct of this specific trial will extend the study design work previously funded through the 2005 C.U.R.E. formula grant.

### **Anticipated Duration of Project**

7/1/2007 - 12/31/2010

### **Project Overview**

The broad objective is to foster the work of a network of academic medical centers in Pennsylvania to perform imaging studies of early phase technology at academic medical centers in Pennsylvania. The American College of Radiology Imaging Network – Pennsylvania (ACRIN PA) presently consists of the University of Pennsylvania, University of Pittsburgh, Hershey Medical Center, Thomas Jefferson University and Fox Chase Cancer Center. The broader initiative seeks to conduct research in three targeted areas: 1) osteoarthritis; 2) cancer; and 3) neurodegenerative disease.

This particular project will focus on a neurodegenerative disease clinical trial originally envisioned as part of the 2005 FY funding. The study design work will be completed with the 2005 FY funding while the actual conduct of a clinical trial will require support from the 2006 FY funding.

The specific aim consists of the conduct of a clinical trial to determine the ability of two novel imaging agents, which target amyloid plaques in Alzheimer's disease patients, to be used for early diagnosis of Alzheimer's disease and/or to monitor the effectiveness of drug treatments targeted at Alzheimer's disease. The proposed trial will compare the quantification of amyloid plaques in Alzheimer's patients using imaging agents developed at the University of Pennsylvania and the University of Pittsburgh in a population of approximately 60 patients to be recruited at those sites. In addition to images collected on these subjects, the study will collect EKG, vital signs, and blood chemistry values to validate that these agents do not produce a pharmacological effect on the body.

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## **Expected Research Outcomes and Benefits**

Through the funding received under the Emerging Imaging Technology Clinical Trials in PA: Part III, the ACRIN PA network will continue to foster multi-institutional clinical trials which allow Pennsylvania laboratories to have their work on new technologies quickly validated in a dedicated multicenter setting, providing them with a competitive advantage over similar work performed at other centers across the world. The network itself could then become an attractive target for pharmaceutical companies initiating additional early phase trials of drugs targeted at arthritis, cancer, and neurodegenerative disease.

The neurodegenerative disease clinical trial described in this project will use novel imaging agents to enable the imaging of proteins associated with Alzheimer's disease (amyloid plaque). If proven effective, these agents will enable early clinical diagnosis (and therefore treatment) of Alzheimer's disease as well as provide an important method for quantifying the extent of disease and, in turn, support more advanced research in determining the effectiveness of new drugs for this debilitating condition.

## **Summary of Research Completed**

### Subject Enrollment – as of June, 2010

The total enrollment goal for the Alzheimer's trials (ACRIN PA 4003-4004) is 30 subjects at each site; 15 controls and 15 with Alzheimer's disease (AD). The excellent progress shown in the table below is a result of expanding the eligibility criteria for subject recruitment. The protocol team, which meets monthly to review trial progress and resolve issues, determined in late 2009 that the accrual rate was too slow due to overly restrictive eligibility criteria. Although the volume of subjects coming through the Alzheimer's clinics at each site remained steady, trial enrollment was not increasing at an acceptable rate.

Institution	Normal Participants	Alzheimer's Participants	Total Accrual
Hospital of the University of Pennsylvania	12	10	22
University of Pittsburgh Medical Center	15	4	19
<b>TOTAL</b>	27	14	41

Within the eligibility criteria, the mini-mental state evaluation (MMSE) score and the clinical dementia rating score were originally designed with extremely tight ranges so as to emphasize the difference between control and AD subjects. The team decided to expand the cognitive dementia rating of a control subject from 0 to 0.5 to remain consistent with other AD research trial criteria, specifically, the Alzheimer's disease Neuroimaging Initiative (ADNI). The protocol was modified, approved by the ACR-IRB, and subsequently approved the sites' IRBs. As a consequence, the pool of potentially eligible subjects increased and accrual has accelerated accordingly.

Other issues discussed and resolved included:

- Non-availability of the AV-45 compound during a location shift by the manufacturing facility.
- Scheduling of scans within one month of enrollment. A protocol modification increased the time from recruitment to completion of scan to three months.
- Required blood testing was not consistent among the two institutions. The protocol was modified so as to achieve consistency in inclusion and exclusion of subjects at both sites.
- Transmission of PET scans to a third party contract research organization (CRO) for quantitative image analysis. The results will be uploaded to the ACR data management center for statistical analysis.

### Qualitative Analysis

The two PET scans per subject will be interpreted by two experts. Their results will be compared with the primary aim of the study which relies upon the quantitative image analysis of eight regions of the brain. In order to ensure common guidelines in interpreting the images, the expert readers compiled a set of 15 test PET scans which utilized the three compounds (<sup>18</sup>F PIB, <sup>18</sup>F AV-45, and <sup>11</sup>C PIB) and interpreted them independently before comparing their results. Using a five point scale, the readers rated the presence of tracer uptake in eight regions of the brain. There was agreement on virtually all of the cases in seven regions of the brain. The disagreement related to no more than a one point spread on four cases in one region of the brain.

### Quantitative Analysis

The quantitative image analysis to be performed by an external contract research organization (CRO) for the 4003 study is presently in progress. Results will be uploaded to the ACR database for analysis by the statistical team.