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14. ABSTRACT This translational research project is based on the epidemiological and preliminary studies demonstrating that omega (ω , n)-3 fatty acids, found in fish oil, may prevent prostate cancer disease progression. Epidemiological studies suggest that intake of n-3 polyunsaturated fatty acids (PUFAs) decrease prostate cancer risk while intake of ω -6 PUFAs, found in plant oils, increases risk. We as well as others have demonstrated that the metabolites of ω -6 and ω -3 PUFAs directly impact PCa tumor development and the ability to do so depend on both diet and the levels of enzymes responsible for metabolizing these PUFAs: Omega-3 metabolites activate anti-tumorigenic pathways and ω -6 metabolites active pro-tumorigenic ones. Moreover, we found that ω -3 PUFAs inhibit the activity of an enzyme central to the synthesis of monounsaturated fatty acids. This fatty acid synthesis leads to increased levels of many proteins, including those involved in PUFA metabolism as well as in other pathways that may affect cancer. Based on the results of our preliminary studies, we hypothesize that ω -3 fatty acid will be highly effective in suppressing growth of human prostate cancer due to it's ability to (a) suppress fatty acid synthesis in the prostate tumor cells (b) inhibit pro-tumorigenic metabolite formation in favor of anti-tumorigenic pathway molecules. In this study, we will treat patients that are diagnosed with prostate cancer with fish-oil containing ω -3 fatty acids or control lipid (oleic acid) for 5 weeks prior to prostatectomy and then use the tissue removed during surgery to precisely identify how ω -3 fatty acids alter the pro- and anti-tumorigenic pathways concomitantly with the phosphoproteins.					
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Introduction

Work from our laboratories and others suggests that the metabolites of dietary omega-3 and -6 polyunsaturated fatty acids (PUFAs) directly affect PCa and the ability to do so depends on intake and metabolic enzyme expression. Omega-3 and -6 PUFAs compete as substrates for cyclooxygenase-2 and 15-lipoxygenase-1, both elevated in PCa; these enzymes convert omega-3 PUFAs to anti-tumorigenic metabolites and omega-6 to pro-tumorigenic ones. PCa cells also have elevated fatty acid synthase (FASN). FASN regulates the expression of a myriad of genes, including the PUFA metabolic enzymes delta-5 and -6 desaturase and phospholipases that liberate arachidonic acid, which together may affect the pool of PUFAs. In addition, omega-3 inhibits FASN, inducing apoptosis in PCa cell lines. We will identify the proteins and modifications involved in PCa specific dysregulation of fatty acid metabolic networks to identify and validate diagnostic and prognostic biomarkers.

The purpose of this study is to evaluate the efficacy of daily oral doses of purified fish oil omega-3 fatty acid in prostate cancer patients scheduled to have a Radical Prostatectomy (RP). Through this study, we will identify an array of proteins, eicosanoids and prostaglandins, and fatty acids and determine how they change in 25 patients on omega-3 fish oil (Arm 1) as compared to 25 patients on oleic acid as a placebo (Arm 2). This study remains an important and timely investigation. Recent reviews have touched on the importance of central fatty acid metabolism (Zadra et al, Clin Ca Res 16(13);3322-8, 2010). There are now 5 NIH funded clinical trials that investigate omega-3 fatty acids in cancer however, none of these trials investigates the links between the anabolic and catabolic fatty acid pathways and our trial remains unique in that pursuit. Our approach not only provides a new paradigm of diet research, but will also generate a comprehensive view of omega-3 effects on prostate cancer, laying the groundwork for omega-3 fatty acids as a promising dietary intervention against PCa. Overall, we expect that our results will : (1) Demonstrate the importance of PUFAs in PCa development; (2) Provide potential targets for treatment based on the metabolic analyses of the prostate tissue, and (3) Identity of unique and distinct metabolomic eicosanoids, prostaglandins, phospholipids and phosphoproteins alterations as markers specifically modulated by dietary fish-oil.

Body

The DoD Synergy Award began in September 2008 and Institutional Review Boards (IRB) for the University of Pittsburgh and the DOD gave final approval for the study in April 2009. In July 2009, Dr. Beth Pflug moved from the University of Pittsburgh to Indiana University School of Medicine in the Division of Clinical Pharmacology and the clinical trial was put on hold until all transfer documents were approved. Shortly after Dr. Pflug's transfer was complete, Dr. Kelavkar took a position at Memorial Medical University and Mercer University School of Medicine, Savannah, GA and Dr. Conrads was recruited to the Molecular Profiling group at the Gynecologic Cancer Center of Excellence. Dr. Kelavkar will continue his research program at Mercer University Department of Laboratory Oncology, however, Dr. Conrads will not be able to continue as Co-PI for the proteomics portion of this study in his new position. The University of Pittsburgh has declined to keep the clinical trial there and we are now working toward transfer of the trial to Indiana University. A formal request and revised research plan was submitted on December 6, 2010 to move the trial to Indiana University School of Medicine. A request of PI change to Dr. Mu Wang, Director of Proteomics at Indiana University has been submitted to transfer Dr. Conrad's responsibilities to Dr. Wang. If the transfer and change of Co-PI are approved, we will begin the trial at Indiana University upon IRB approvals. The Research Coordinator, Jill DeLuca, has already prepared the documents for IRB submission at Indiana University. The fish oil and oleic acid capsules for the entire study have been formulated, quality tested, packaged and shipped by KD Pharma Bexbach GmbH to the University of Pittsburgh Pharmacy Services and these capsules will be sent to Indiana University Pharmacy Services for distribution to the patients in the study. All the members involved in the trial are in regular contact either via e-mail and/or telephone calls with updates if any.

KEY RESEARCH ACCOMPLISHMENTS: Not applicable (N/A)

REPORTABLE OUTCOMES: None.

CONCLUSION: We have submitted the request to move the clinical trial to Indiana University School of Medicine. The transfer request document included a letter requesting that Dr. Mu Wang assuming responsibility for the proteomics portion of the study and his background and qualifications. Also included was our modified research plan, letters of support from the Urologist, Pathologist, Statistician, Nutritionist and Chair of Radiation Oncology for their roles in this study, budgets, biosketches and other supportand modified clinical trial documents.

REFERENCES: N/A

APPENDICES: N/A **SUPPORTING**

DATA: N/A