RESEARCH STRATEGY

1. Summary of Parent Award

This is a proposed supplement to R01-CA189184 titled: "Discovery and verification of novel biomarkers of colorectal cancer recurrence". Below is the abstract of this parent award:

In order to realize the promise of precision medicine, more and better biomarkers are needed to guide clinical decision making. This is of particular importance for patients with colorectal cancer (CRC) as: 1. CRC is the third most common cancer in both men and women accounting for 9% of all incident cancers in the United States; 2. The 5-year survival rates for the most common cancers in men and women, prostate and breast cancer, are 99% and 89%, respectively, but is only 64% for CRC making it the second most common cause of cancer related death in the U.S.; 3. At present there is a lack of clinically useful biomarkers predictive of recurrence or survival for CRC patients that can be used to guide surveillance and treatment. Consequently, there are issues of both overtreatment and undertreatment because treatment is based largely on clinical and pathologic parameters, but little else to risk stratify patients. This study will utilize 1,574 participants in a multi-center prospective cohort (the ColoCare Study) of newly diagnosed CRC patients. Detailed demographic, clinical, epidemiologic, and follow-up data are ascertained on all participants along with blood samples collected at multiple time points. Thus, this study is specifically designed to meet the overarching goal of this proposal, the discovery and verification of novel blood-based biomarkers predictive of recurrence among CRC patients, through achieving the following specific aims: **1. Discovery and verification of novel biomarkers predictive of recurrence among CRC patients:** Utilizing samples collected at the time of diagnosis we will evaluate the plasma proteome, glycome, and autoantibody repertoire, including assessment of promising markers reported in the literature, using well-validated laboratory approaches to identify markers predictive of risk of recurrence for well-defined clinical applications (predicting recurrence in stage I/II patients and in stage III patients). Top candidates from our discovery experiments meeting particular statistical criteria will be evaluated in a group of patients completely separate from those used in the discovery set. **2. Discovery and verification of novel biomarkers useful for the early detection of CRC recurrence:** Utilizing serial samples collected at regular intervals post-diagnosis we will discover novel biomarkers potentially useful for disease monitoring using proteomic, glycomic, and autoantibody platforms. Markers will be evaluated in the context of CEA, a clinically used biomarker of recurrence that has a 60% sensitivity and 90% specificity for detecting recurrent colorectal cancer in stage II and III patients. If successful this project could lead to the development of clinical grade biomarker assays that could have significant impact on reducing the morbidity and mortality associated with colorectal cancer. This study is innovative in that the cohort that will be used is unique, highly characterized, and possesses serial samples collected at regular intervals; the unique platforms that will be used have been shown to yield potentially useful biomarkers and can also evaluate existing markers of interest; and this study is powered to identify biomarkers with clinically meaningful performance characteristics.

2. Proposed Supplement Activities

The overarching goal of the parent grant is to discover and verify novel blood-based biomarkers of CRC recurrence. An important supplement to this effort is characterizing how various epidemiologic and clinical factors impact risk of CRC recurrence and how they may interact with the blood-based biomarkers identified. Ms. Y is ideally suited to play a key role in this effort given her current training in epidemiology under Dr. X's mentorship. This supplement will have two primary specific aims:

1. Evaluation of how various epidemiologic and clinical factors impact risk of CRC recurrence within the prospective ColoCare Study cohort: While there is some evidence that various epidemiologic (e.g., body mass index, physical activity, co-morbid conditions, glycemic load, etc.) and clinical factors (e.g., age at diagnosis, tumor size, nodal status, etc.) may be related to risk of CRC recurrence most of the published literature is based on small studies an results are somewhat inconsistent. The ColoCare Study is an ideal setting to further evaluate these risk factors given its rich collection of data from both patient questionnaires and medical records.
2. Evaluation of how epidemiologic and clinical factors interact with the novel blood-based biomarkers discovered in the parent grant with respect to predicting risk of CRC recurrence: We hypothesize that epidemiologic risk factors and clinical factors may modify the relationships between different biomarkers and risk of CRC recurrence.

Both of these aims involve utilization of the self-reported data and the data abstracted from medical records collected by the ColoCare Study. The overall design of ColoCare is summarized in Figure 1.

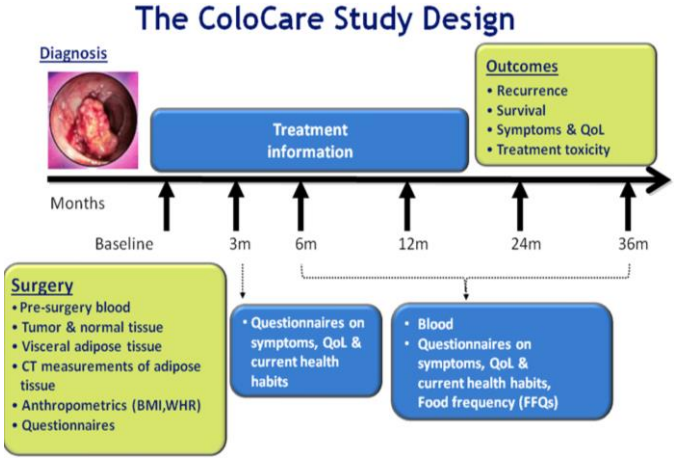

Figure 1. ColoCare Study Design

Briefly, participants are asked to complete questionnaires on health behaviors, symptoms and quality of life at baseline and at months 3, 6, 12, 24, 36, 48, and 60 of follow-up. The baseline questionnaire completed at diagnosis ascertains data on a variety of potential risk factors including family history, medical history, medication use, and lifestyle characteristics. It includes measurement of height, weight, and waist and hip circumferences. The follow-up questionnaires collect updated information on several of these exposures and additionally collect information on treatments and symptoms resulting from various treatments. Baseline questionnaires are completed by 100% of study participants and follow-up questionnaires are completed by 85-95% of study participants.

Medical record reviews are conducted at least two years post-diagnosis on all patients to ensure that any recurrences diagnosed within two years of diagnosis, the time frame over which the vast majority of CRC recurrences present (~80%), are captured. Additional information that sought through these reviews are detailed data on all CRC treatments received including timing and dose, pathologic features and molecular testing of tumor tissue samples [so cases can be stratified according to pathologic and molecular subtypes; of note the majority of ColoCare patients have their tumors evaluated for both MSI status and CpG island methylator phenotype (CIMP)], and information on follow-up testing to monitor for disease recurrence including CEA test results and imaging results. These medical record reviews are conducted by highly experienced medical record abstraction teams at each site. Clinical follow-up through at least two years are available for 100% of study participants since these data are ascertained from medical records through consent provided at the time of initial enrollment, and we also have experience obtaining records by mail from non-local clinics/hospitals if patients move.

Ms. Y will lead all analyses and manuscripts pursued through this supplement. She will assess factors that predict risk of CRC recurrence by conducting Cox proportional hazards modeling. Date of diagnosis will be the time of entry for all cases who will then be followed for the development of a CRC recurrence. Cases will have a variable follow-up time ranging from a maximum of 5 years to a minimum of 2 years with an average follow-up time of ~3.5 years per participant. For Aim 1, all of the primary exposures of interest (epidemiologic and clinical) will be assessed to evaluate the performance of individual and combinations of exposures in terms of sensitivity and specificity to predict risk of recurrence. For Aim 2, interaction terms with various risk factors and blood-based biomarkers will be assessed using Cox proportional hazards modeling.

3. Plan for the Candidate to Interact with Other Individuals on the Parent Grant

The original ColoCare sites include the Fred Hutchinson Cancer Research Center (FHCRC, Seattle, WA), the Moffitt Cancer Center (MCC, Tampa, FL), and the German Cancer Research Center (DKFZ, Heidelberg, Germany). ColoCare has expanded to four new sites through the recently awarded U01-CA206110: “Transdisciplinary Team Science in Colorectal Cancer: the ColoCare Study”. These new sites were selected to expand the racial/ethnic diversity of the cohort and include: Cedars-Sinai/USC (Los Angeles, CA), Washington University (St. Louis, MO), and the University of Tennessee (Memphis, TN). Given its size, ColoCare has a well-developed infrastructure to promote interactions that includes monthly teleconferences and an annual in-person meeting. Ms. Y will be invited to attend all of these meetings. Additionally, ColoCare has a mechanism in place to propose ancillary projects. The work proposed by Ms. Y has been conditionally approved (pending the funding of this supplement) and will include collaborations with investigators across each participating site. Thus, Ms. Y will have the opportunity to interact deeply with investigators across the ColoCare Consortium.

4. Plan for the Candidate to Contribute Intellectually to the Research

Ms. Y will provide key intellectual contributions to the proposed research by taking the lead role on analyzing all of the data relevant to the specific aims proposed here. She will also serve as the first author of all publications stemming from this work.

5. Plan for the Candidate to Enhance her Research Skills/Capability and Knowledge Regarding the Selected Scientific Area

This project will greatly expand Ms. Y's knowledge of colorectal cancer and her research skills. She will spend the first few months of this supplement increasing her knowledge of colorectal cancer and risk factors for CRC recurrence. She will then plan analyses in support of this supplement's two specific aims beginning with Aim 1. This work will give her hands-on experience conducting epidemiologic statistical analyses specifically using Cox Regression, which she has learned in class but not applied to real-world data. She will then lead the interpretation of the data generated and with Dr. X's mentorship will serve as the lead author of all resulting manuscripts. It is anticipated that by the end of this supplement Ms. Y will have at least two first authored publications.

6. Opportunities that will be Provided that will Contribute to the Student's Career Development as a Productive Researcher

Ms. Y will be provided with a number of opportunities that will advance her career development. First, she will have the opportunity to learn about and contribute to the detailed operations of a large multi-center prospective cohort study. As shown in Figure 1, the ColoCare Study involves a comprehensive evaluation of all enrolled participants with data ascertained from multiple sources: patient self-report, medical record abstractions, and genomic/molecular/biomarker data from patient biospecimens. Understanding how to execute a study involving primary data collection is critical for all epidemiologists in training as it is important to understand the strengths and limitations of the data generated. Ms. Y will also interact with epidemiologists and physician-scientists throughout the ColoCare Consortium with opportunities to learn from those who will collaborate with her on this project. These connections will expose her to a broad range of scientific areas of expertise, but also help her grow a network of collaborators throughout the country that could serve her well in the future as she considers next steps such as potential post-doctoral fellowships or junior faculty positions. Lastly, the research projects themselves that Ms. Y will work on will provide her with invaluable experience with respect to analyzing and publishing epidemiologic data. This will certain strengthen her CV and position her well for her next career transition.

7. Mentoring Plan

Dr. X will serve as Ms. Loroña's primary mentor. Dr. X is the co-Head of the Translational Research Program at FHCRC and a Research Full Professor in the Department of Epidemiology at the University of Washington. He has a long track record of mentoring trainees at various levels having chaired 14 Masters thesis committees and 6 PhD dissertation committees and supervising 6 post-doctoral fellows. Several of his trainees have gone on to obtain independent faculty positions at various institutions including the University of Washington, Seattle Children's Hospital, the University of British Columbia, the University of New Mexico, and the Roswell Park Cancer Center. He also has an outstanding track record of independent research as he is currently MPI of three NCI R01's and two NCI U01's and has over 150 peer-reviewed publications. Of note, while he was a post-doctoral fellow and a junior faculty member he received a minority supplement and a K01-award through the NCI Center to Reduce Cancer Health Disparities' (CRCHD) CURE (Continuing Umbrella of Research Experiences) Program. He has maintained ties with CRCHD and has demonstrated a strong and sustained commitment to both cancer disparities research and increasing the diversity of the cancer research workforce. In particular, he has served as both member and chair of the Minorities in Cancer Research Council (MICR) of the American Association for Cancer Research (AACR), and has chaired AACR's Science of Cancer Health Disparities Conference three times, most recently at this conference's 10th meeting in 2017.

Dr. X is strongly committed to Ms. Y's career development. He will meet with her at least twice monthly to review her progress, go over data she generates, and provide general mentorship related to career development. There will be two primary phases to this supplement. In the first, Ms. Y will focus on expanding her knowledge of colorectal cancer, colorectal cancer recurrence, and the ColoCare Study. This will involve reviews of the literature, learning from and engaging ColoCare Study staff, and reviewing all ColoCare study documents and protocols. The second phase will focus on finalizing an internal ColoCare ancillary study proposal detailing the specific data items and analyses that Ms. Y will conduct and then completing this

work. Both phases will be conducted under Dr. X's supervision and mentorship. Additional FHCRC staff that will be available to support Ms. Y include Ms. W , the FHCRC ColoCare Study Coorinator, and Dr. Z , the statistical research associate who oversees the ColoCare data repository.

Milestones:
It is anticipated that over the course of this supplement Ms. Y will complete the following milestones:

1. Gain a deep understanding of the epidemiology of colorectal cancer and colorectal cancer recurrence
2. Develop strong relationships and collaborations with ColoCare investigators at other sites
3. Translate skills learned in the classroom to the real-world setting of the ColoCare study with respect to expanding knowledge/skills related to study design, study implementation, data collection, statistical analysis, and manuscript preparation
4. Present an abstract at at least one national conference (e.g., the AACR Annual Meeting)
5. Publish at least two first authored papers using ColoCare data
6. Complete her Master's degree and be accepted to a PhD program