**SPECIFIC AIMS**

There are an estimated 14,000 annual deaths due to renal cell carcinoma (RCC) in the United States, making this disease the urologic malignancy with the highest mortality. The incidence of RCC has risen at an alarming rate in African-Americans and now is 30% greater than Caucasians. African-Americans also have a worse RCC outcome than any other race for unclear reasons. While various studies have found that African-Americans less frequently receive standard kidney cancer systemic and surgical management, even when controlling for treatment, survival disparities still exist. Beyond access to care barriers, similar to other urologic malignancies such as prostate cancer, biologic differences in disease characteristics may account for racial disparities in kidney cancer. Recent studies have shown that African-Americans present at a significantly younger age than Caucasians. Early disease onset is something in RCC considered a possible indicator of a hereditary predisposition. Another key disparity between races is that the histologic distribution is drastically different in African-Americans. While clear cell RCC (ccRCC) is the most common histologic type in all races, papillary RCC (pRCC) is three-fold more common in African-Americans, accounting for 35-40% of cases. Unfortunately pRCC has been understudied and there are no current forms of effective systemic therapy for this disease. With significant racial disparities present in kidney cancer, we set out to identify possible genomic alterations explaining these cancer disparities. To do so, we will analyze available genomic data contained in the Cancer Genome Atlas (TCGA) kidney cancer cohorts. Since there was a scarcity of African-American subjects with ccRCC included in the TCGA, additional whole genomic sequencing on Yale African-American subjects will be needed to fill out the dataset and make appropriate comparisons across race and the major histologic subtypes. Both coding and non-coding as well as germline and somatic variations associated with RCC will be identified and compared between race and subtype to help identify the genomic basis of kidney cancer racial disparity.

**Hypothesis:**We hypothesize that 1) recurrent non-coding as well as coding germline and somatic alterations are associated with kidney cancer and 2) specific germline and somatic alterations are more common in African-Americans with kidney cancer. We will test our central hypothesis with the following aims:

**Aim 1: To perform whole genome sequencing (WGS) of African-Americans with ccRCC to complete a missing aspect of the cancer genome atlas (TCGA).** WGS will be performed on a consecutive series of Yale African-Americans patients with ccRCC, using sequencing parameters similar to those in TCGA, to provide a cohort useful for comparing genomic alterations between race (Caucasian vs. African-American) and histologic subtype (ccRCC vs pRCC).

**Aim 2: To assemble a set of coding and non-coding regions associated with kidney cancer, both in terms of somatic and germline alterations.** We will analyze the African-Americans with ccRCC sequenced in Aim 1 as well as existing TCGA RCC cohorts to identify key genomic regions (and collections of regions, notated as modules) associated with kidney cancer. Novel pipelines for evaluating functional impact and germline and somatic mutational burden will consistently prioritize coding and noncoding regions.

**Aim 3: To identify genomic regions differing most between African-Americans and Caucasians with kidney cancer.** We will analyze genomic regions and modules developed in Aim 2 to identify racial differences in the occurrence of common SNPs or in terms of differential burdening with rare, germline or somatic alterations. We will prioritize and rank many (~500) genomic regions with the highest scores, indicating a possible a hereditary predisposition to kidney cancer.

**Aim 4: To validate specific regions with either germline or somatic mutations suspected of contributing to kidney cancer racial disparity.** We will utilize an independent cohort of African-American and Caucasians patients treated at Yale with ccRCC and pRCC. Tumor and normal DNA will be assessed with a PCR-Mass spectroscopy based system to evaluate candidate genomic regions identified in Aim 3.

**Deliverable:** We plan on developing a coherent data resource for the investigation of racial disparities in kidney cancer. The resource will include variant calls for the Yale cohort consistent with TCGA methodology. It will also have a tabulation of coding and non-coding regions associated with kidney cancer, a ranking of them in terms of potential racial disparity and validation results for the most disparate regions.

**Summary:** Significant racial disparities exist in kidney cancer with African-Americans having increased cancer incidence, earlier age of onset, a different subtype distribution, and worse survival. While multiple studies have characterized epidemiologic differences, to date, there has been no comprehensive investigation into a biologic or genetic cause of this cancer health disparity. *Our proposed research plan will improve our understanding of the genomic cause of racial disparity in RCC and may have implications beyond the scope of this project. We anticipate the findings will provide insight into inherited cancer predisposition and acquired driver alterations in African-Americans with RCC.*