**Response to Panel and Reviewers’ Comments of Previous Submission**

[[We submitted this proposal in 2015. In the review, we were]] We are pleased that the panel characterized the investigatory team and environment as “*excellent”*, “*highly experienced and qualified*”, and our proposal as “*well thought out..* *as regards the recruitment of the AA patients*”, with “*novel concepts, hypotheses* and *bioinformatics*”. We thank the reviewers for their thoughtful and constructive criticisms, which we address below and in our revised grant:

**Stratification and pre-selection of Genomes.** One of the panel’s major concern was data stratification. R#1 asked “*how the variants will be segregated or ruled out of analysis..* ”. R#2 noted that the absence of a planned enrollment report made it “*difficult to ascertain the ethnic distribution*”, while R#3 pointed that our proposal *“failed to stratify patients ... mechanisms may vary”*. (A) We have included an updated version of LARVA (NIMBus) that identifies mutational burden, while regressing on multiple factors that might influence the mutation rate across individual genomes. (B) We have added two genotyping analyses, in order to genetically confirm the ethnicity as well as improve the comparison between our tested groups in Aims I and IV. Finally (C), we have now added in Aim II C-2-c-5, details for our stratification plan for burdened germline regions. [[more+additional seq.]]

**Biological and Clinical implications.** The panel discussed the absence of extended discussion concerning the ccRCC and pRCC mechanisms. R#1 noted that “*there is a gap between .. mutations and clinical features*”. R#3 added that “*the current knowledge of genetic mechanisms and biological factors .. should have been provided*”. To respond: (A) In a recent work, we scrutinized the whole genomes of pRCC and found many interesting alterations linked with both biological factors and clinical features such as prognosis. Those novel findings potentially transform into actionable clinical implications (see C-2-b-3),(B) We have now included two more analyses including the study of loss of function mutations, as well as examining the prevalence of deleterious mutations. Finally (C), to strengthen our proposal, we provide preliminary results from 14 genes associated with kidney cancer with a heavier inherited mutational burden in the germline of African-Americans.

**Improving Deliveries for Specific Aims.** Some reviewers expressed their concern for the degree of aim-independence and the significance of their respective deliverables. R#3 noted that *the success of Aim 3 is dependent on Aim 2, and Aim 4 on Aim 3*. We feel that the inter-connected nature of our aims strengthens our proposal, reflecting its cohesiveness. However, we have revised our deliverables in a way to provide more useful work product that stands on its own. We have increased the significance of our intermediate deliverables by including a) a loss of function analysis, b) mutational signatures, c) the study of regulatory networks burdened by somatic and germline mutations, while we d) plan to compare the mutational burden between different ethnic groups with respect to the ExAC database and 1000 genomes database.

**Providing Additional Preliminary Results.** Concern was raised for supporting preliminary results. We now include an additional figure showing that important for the development and progression of Kidney cancer gene regions are racially burdened with deleterious mutations.

**Providing additional Controls.** Concern was also raised by the panel for the lack of control datasets. R#3 suggested that “*the experimental design lacked controls; it is not enough to use TCGA controls…”*. We have now included in Aim IV the validation of additional control regions.