2025 MCC Community Outreach and Engagement Pilot Project Award

Cross-ancestry investigation of host factors linked to telomere length and lung cancer risk

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Scientific Abstract:

Immunotherapies have rapidly been adopted as a standard of cancer care. However, response rates remain low for some tumor types, and evidence suggests there may be ancestry-associated differences in potential to benefit, even when controlling for social and economic factors. Our work has uncovered host genetic variants that modify immunotherapy response, implicating gene regulation as a mechanism of resistance. Our preliminary studies identified a common variant in the 2nd intron of *TERT* as associating with reduced *TERT* expression and T cell dysfunction in lung adenocarcinoma, a disease the disproportionately affects Hispanic persons in the Moores Cancer Center catchment area. *TERT* regulates telomere length (TL), which is a determinant of tumor fitness and T cell function and has been shown to vary across populations. Thus, TL could be a potential mediator of differences in immunotherapy response. *POT1* is another component involved in maintaining telomeres implicated in cancer. This proposal will investigate common variants affecting TL via two genes, *TERT and POT1,* both known to play key roles in lung cancer. We hypothesize that variants affecting *TERT* and *POT1* gene regulation will generate differences in TL length distributions in proliferating lung cancer cells. We will analyze variants across ancestries to implicate putative regulators of *TERT* and *POT1* gene expression, then assay these variants in lung cancer cells to measure their effects on gene expression, proliferation, and telomere length. These experiments will provide preliminary data to support future funding applications to investigate *TERT* and *POT1* regulatory variants in cancer progression across genetic backgrounds.

Lay Abstract:

Inherited genetics influence disease risk and treatment responses. We are interested in studying genetic variation affecting two genes, *TERT* and *POT1*, associated with telomere length. Telomere length has been associated with cancer cell fitness and immune cell function, and we hypothesize that genetic variants affecting the regulation of telomere length will contribute to inter-individual anti-tumor immune responses and response to immunotherapy. Both telomere length and immunotherapy response have been reported to differ across ancestries. In this proposal, we plan to focus on identifying and experimentally validating variants that regulate the expression levels of *TERT* and *POT1,* grouping them according to potential to increase expression and therefore increase tumor cell fitness, or decrease expression and therefore impair anti-tumor immune responses. Where possible, we will seek to collect evidence that these variants affect immunotherapy outcomes. Our findings will set the stage for future studies and funding applications to pursue biological mechanisms contributing to inter-

individual variation in benefit from immunotherapies. Our long-term goal is to use this information to better match diverse cancer patients to therapies they can benefit from and to inform design of more effective immunotherapies.