CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP180248

Project Title:
Characterizing cancer genome instability and translational impact using new sequencing technologies

Award Mechanism:
Individual Investigator Research Awards for Computational Biology

Principal Investigator:
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Entity:
The University of Texas M.D. Anderson Cancer Center

Lay Summary:

Genome instability is a hallmark of cancer. Cancer cells with homologous recombination deficiency (HRD) often exibit a high level of chromosomal instability containing relatively large numbers of structural variations (SVs). Patients with homologous recombination deficiency (HRD) tumors have been shown to respond to Poly (ADP-ribose) polymerase (PARP) inhibitors. Meanwhile, cancer cells with mismatch-repair (MMR) deficiency often have high mutation (indel) burdens. Patients with MMR deficient tumors (e.g., melanoma and lung cancers) have demonstrated durable clinical responses to cancer immunotherapy such as CTLA-4 or PD-1/PD-L1 blockade. Still, a large fraction of patients were not benefited from these therapies, due partly to deficient characterization of genome instability. Thus, developing computational methods that enable comprehensive and accurate genome instability characterization will extend the clinical benefits of immunotherapy and PARP inhibitors to many cancer patients.

In this proposal, we aim to develop a set of novel computational methods to achieve 1) sensitive indel/SV detection using a combination of next generation sequencing (NGS) and third generation sequencing (TGS) technologies, and 2) more accurate clonal heterogeneity and allele-specific copy number calculation via integrated analysis of germline and somatic variants. These efforts will lead to accurate identification of neo-antigens and calculation of HRD scores. We will examine our approaches using TCGA and several clinical trial data collected at MD Anderson cancer center. We will also experimentally test novel neo-antigens identified by our algorithms using a unique set of melanoma cell-line and patient-matched tumor infiltrating lymphocyte (TIL) libraries.

In summary, this proposal will develop computational methods to achieve comprehensive accurate characterization of genome instability and maximize the clinical benefit of immunotherapy and PARP inhibition.