A Massively Parallel Protein Synthesis Platform for Functional Screening of Cancer Proteomes

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Abstract: Human serum contains a complex mixture of antibodies that recognize diverse epitopes. Antibodies can target foreign proteins, such as virus-encoded proteins, and can also target endogenously synthesized proteins. Antibodies that target endogenous proteins can lead to pathologic responses such as graft-versus-host disease, autoimmune disease, and paraneoplastic diseases. In some cases, antibodies recognize “neo-epitopes” that are uniquely expressed in cancer cells as a result of cancer-associated genomic mutations. A major challenge is identifying the targets of these auto-reactive antibodies. This technology development application describes the optimization of a novel platform for rapidly and efficiently synthesizing fragments of proteins encoded by the cancer genome on a flow cell. We have developed an approach that modifies the Illumina deep sequencing platform, which normally produces DNA sequence data, so that the DNA is converted to RNA and then to the encoded protein. The encoded protein fragment is present on the Illumina flow cell in clusters, each linked to a specific DNA sequence. We describe experiments to use these cancer cell proteomes displayed on the Illumina flow cell to interrogate the serum antibodies derived from patients who have been treated with cancer immunotherapy to treat melanoma. We will address the longstanding question of whether cancer immunotherapy involves the formation of antibodies to cancer-specific mutations. Overall, this approach will result in a novel methodology to define the reactivity of serum antibodies which will have a broad impact in our understanding of therapeutic and pathologic auto-antibody responses.