Host Cofactor Fitness Profile of the HIV-1 Genome

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In this proposal we will utilize a novel genetic platform that we have developed to functionally profile the entire HIV-1 genome to define virus-host interactions. We will determine the increase or decrease of sensitivity to two different host cellular proteins that have opposing effects on viral replication, specifically B-lymphocyte kinase, a protein that positively influences replication, and interferon-induced transmembrane protein 3, a protein shown to inhibit replication. Our genetic platform has the capacity to assess every nucleotide position in HIV-1 in all genomic space (all possible base change mutations). We have already detailed a viral replication fitness map of HIV-1 in our preliminary studies that successfully shows we are capable of achieving this level of resolution. The fitness map will be used to identify genomic stretches that are intolerable to mutation – information that will be highly useful for HIV-1 vaccine development. The implications of our study are far reaching. To our knowledge, no group has undertaken such a comprehensive genomic survey of any pathogen. We aim to further our studies by applying our technology to quickly and efficiently map HIV-1 genomic regions implicated in cofactor interactions with no prior knowledge of where in the genome the interaction may be located. The identification of new host-HIV-1 protein-protein interactions will provide a wealth of new target sites for the rational design and development of novel HIV/AIDS therapeutics useful for clinical evaluation.