CALIFORNIA HIV/AIDS RESEARCH PROGRAM

Longitudinal Imaging of Early HIV Infection *in situ*

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Over 130,000 individuals are estimated to be currently living with HIV/AIDS in California. Many newly infected individuals do not realize they have HIV until several weeks later when they may present with flu-like symptoms and high levels of virus in the blood. At this point, the virus has already established productive infection and spread to the major disease sites in the body. Lymphoid tissues (gut, spleen, lymph nodes) contain large concentrations of immune cells and are the locations where most HIV/AIDS-related pathogenesis occurs. Little is known about the early stages of HIV infection when the virus spreads from the initial site of transmission to lymphoid tissue sites throughout the body. The goals of this study are to combine new microscopic imaging techniques with emerging animal models of HIV infection to visually define how individual virions and infected cells establish productive infection, and to understand how early stages of infection proceed within lymphoid tissue.

Recently developed animal models of HIV-infection enable studies of HIV-infection in an environment similar to that of an infected patient. "Humanized" mice, for example, allow repopulation of immune-deficient animals with human immune cells, which have successfully recapitulated important aspects of HIV/AIDS from infected patients, including systemic virus spread, immune cell depletion, and development of AIDS-like symptoms.

Advances in light and electron microscopy allow three-dimensional analysis of tissues at previously unattainable levels of volume and resolution. Light sheet fluorescence microscopy generates a thin plane of light to optically section tissue samples at high speed and at single-cell resolution, providing imaging of entire organs at single-cell resolution. Three-dimensional electron microscopy provides tissue imaging at sub-cellular resolution, identification of individual HIV virions, and delineation of the spatial relationships between virions and infected cells within tissue. The combination of both light and electron microscopy analysis can correlate multiple levels of volume and resolution.

Our proposed studies aim to infect "humanized" mice with HIV and to utilize advanced 3D light and electron microscopy techniques to image HIV-infected lymphoid tissue over time as the virus spreads from the initial site of infection to distant locations. These studies will allow the direct visualization of HIV-infected cells and individual virions in lymphoid tissue at multiple levels of volume and resolution during the establishment of productive infection, in order to identify routes of virus spread, localize reservoirs of virus and infected cells over time, and probe underlying biological mechanisms of virus spread. They will also identify future targets to be explored for therapeutic benefit and will be directly translatable to other animal studies and the analysis of samples from HIV-infected patients.

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