CALIFORNIA HIV/AIDS RESEARCH PROGRAM

The Role of CD28 Family Receptors/Ligands in AIDS-Lymphoma

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Lymphoma, a cancer of the immune system, occurs much more frequently in people who have HIV infection compared to healthy, uninfected, people. Although the rate of AIDS-lymphoma has dropped since the advent of effective drugs against HIV, it still remains much higher than the rate of lymphoma in the general population. Although more effective treatments for this cancer have become available in recent years, there is still considerable room for improvement, as many people still die of this disease in the long term, including in California. Recently, we have determined that cells of many ARL tumors have on their surface certain molecules (CD28, PD-1, and PD-L1) that may fuel their growth, make them more resistant to chemotherapy, or stop the immune system from attacking them. In the proposed pilot studies, we hypothesize that blocking these molecules with drugs will stop tumor growth. In a first set of studies, we will examine expression of these molecules on a wide variety of ARL specimens obtained from pathology labs. We will also examine what these molecules do in experiments in which cells from ARLs are grown in culture. We have also developed mouse models of ARL in which human ARL tumors grow in mice. Tumors in these mouse models closely resemble human ARL. Since experiments in cell cultures sometimes do not show everything that is going on in actual tumors in humans or animals, we will perform studies of the cell surface molecules (CD28, PD-1, PD-L1) in our mouse models to gain a fuller sense of what these molecules are doing. Drugs are available that can inhibit these cell surface molecules, and we will inject these drugs into mice with ARL tumors and determine if they will inhibit tumor growth, make tumors more susceptible to traditional chemotherapy, or make tumors more susceptible to chemotherapy. We think that, given our preliminary data, there is a significant likelihood that these studies will be successful. If so, we will use the data from these studies to apply for more comprehensive funding for studies in this area from other sources. The successful completion of the proposed studies could lead to new treatments for ARL. We note that in the last several years drugs targeting the PD-1 and PD-L1 have shown amazing success in treating a variety of tumors. It seems likely that these drugs could be used to treat ARL, as well.

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