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### **Contributions of Human Endogenous Retroviruses to Metastatic Melanoma Progression: A Potential Novel Treatment Target**

One of the surprising findings from the sequencing of the human genome was the revelation that nearly 8% of the human genome encodes endogenous retroviral elements (HERV). It was once thought that endogenous retroviruses are just genetic artifacts of retroviral infections experienced millions of years ago, however mounting evidence indicates that these ancient genetic elements are still active and may be involved in a variety of diseases. Unlike the common cold or influenza, retroviral infections (the most famous example being HIV) are not temporary. Retroviruses insert their genetic sequences into the DNA of the infected organism becoming a permanent addition to the 'host' (human) genome.

Given the ability of retroviruses to alter host DNA it is not surprising that HERV elements have been suggested to participate in the pathogenesis of several human cancers (including cutaneous melanoma (M), breast, lymphoma, prostate, and renal cancer). In fact, the association of melanoma with retroviruses dates to the 1970s when viral particles were visualized in human melanoma cells using an electron microscope. Recently, petri dish and mouse experiments have suggested a significant role for HERV activity in the proliferation and immune suppression associated with human melanoma. A fascinating series of studies have shown that the role endogenous retroviruses may play in melanoma can be modified.

Like all retroviruses, HERVs require an enzyme called reverse transcriptase which allows the viruses' RNA to be reverse-transcribed into DNA, which then inserts into the host genome. The reverse transcriptase enzyme has been a wonderful target for HIV medications and it is this class of anti-retroviral drugs (non-nucleoside reverse transcriptase inhibitors, NNRTI), which have been found to significantly reduce proliferation of melanoma cells and also increase the expression of an important immune protein, HLA-I. In a striking mouse study, NNRTIs were able to reduce the size of melanoma tumors by more than 50% when compared to untreated mice.

While mouse studies are an important step in the discovery of novel therapies for human diseases, it is encouraging to find evidence that experimental data in model systems can be representative of human disease. Epidemiological data from Australia suggests that HIV+ individuals treated with anti-retroviral medications display a significant reduction in melanoma incidence when compared to the general population, even in the context of their immunosuppression. While this is certainly not a controlled human study testing the effects of NNRTIs in melanoma patients, it may suggest that anti-retroviral drugs can modify the biology of melanoma.

Our hypothesis is that endogenous retroviruses influence the anti-melanoma immune response and also the ability of melanoma cells to regenerate. If human endogenous retroviruses contribute to the cancerous phenotype, a rational therapeutic approach would be to activate an

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anti-retroviral state. Interestingly, the first-line treatment options for melanoma are immunostimulants, including interferon-alfa-2b which possesses potent anti-retroviral effects. The University of Pittsburgh Cancer Institute's Melanoma Program has organized and conducted several large clinical trials utilizing interferon-alfa-2b which has allowed the collection of thousands of human samples. We aim to clarify the relationship between interferon-alfa-2b treatment and human endogenous retroviruses in melanoma by leveraging the extensive clinical sample bio-bank of the University of Pittsburgh Cancer Institute's Melanoma Program. We would also like to explore the anti-melanoma activity of currently available anti-retroviral agents in hopes of identifying a novel treatment modality.

We will first quantify the levels of endogenous retroviral RNA and proteins in melanoma patient samples. We will then assess whether the quantity of endogenous retroviral material correlates with the clinical outcomes. Finally, we will conduct cell culture experiments designed to detect a difference in proliferation and immune protein expression in melanoma cells that are exposed to anti-retroviral medications.