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PROJECT: Biologic Local Control in Xenograft Models of Pediatric Bone Tumors Using Ocolytic Herpes and anti-VEGF Antibodies

Objective:
Osteosarcoma (OS) and Ewing Sarcoma (ES) are the two most common cancers of bone, and occur commonly in arm and leg bones. Currently these cancers are treated by extensive surgeries in addition to chemotherapy drugs. With modern surgical techniques, arms and legs can usually be saved, but occasionally the limb needs to be amputated. We seek to develop a new therapy for bone tumors that might be able to replace the need for surgery. We propose to inject tumors with a virus, which has been intentionally hampered so it no longer causes disease. In addition, it is known that new blood vessel formation is important in these bone cancers. Our objective in this project is to test the combination of a herpes virus with medicines that prevent new vessel formation to cause the tumor to disappear.

Rationale:
Variants of natural viruses have been constructed to be unable to infect normal cells, but can infect cancer cells. These viruses multiply within a cancer cell and destroy it. They then spread to the next cancer cell and so on, until the whole cancer is destroyed. These viruses have proven to be safe and are currently in clinical trials, mainly for brain cancers.

The virus used is called rRp450, a herpes virus mutant. We have shown in our lab that this viurs is able to kill tumors from osteosarcoma and Ewing sarcoma growing in mice. In the test tube, we are able to achieve complete kill of the cancer cells, but when we let these tumors grow in mice, the viruses are incapable of completely curing these cancers. Therefore, there must be something in the living animal that prevents the viruses from achieving complete tumor cure. Other scientists have shown that when herpes viruses are injected with tissues, they cause immune cells to respond to the virus infection by attacking infected cells. These immune cells produce a substance called vascular endothelial growth factor (VEGF). VEGF helps cause new blood vessels to form that feed the tumor. By blocking VEGF, we think we will decrease blood vessel formation that feeds the cancer. We might also decrease the immune effects on the virus. These combined effects should lead to a better ability of the virus to fight off the cancer. In this project, we will test virus in combination with a drug called bevacizumab, which blocks VEGF. This drug has been approved by the FDA for the treatment of colon cancer and lung cancer.

Methods:
We will use mice that have osteosarcoma and Ewing sarcoma tumors. These mice will be given injections of bevacizumab twice weekly, followed by two injections of rRp450 virus. Instead of bevacizumab, on group of mice will be given a non-specific antibody only (as a placebo) and another group will receive rRp450 virus only. These mice will be followed up in time by measurements of their tumor sizes. We will also check the tumors under the microscope to verify changes in the new vessel formation.

Expected Results:
We predict better cancer control in the combination treatment group compared with the single agent treatment groups. We also expect to find suppression of new vessel formation in the groups given the anti-VEGF drug. The findings from this study might open up a whole new way of treating patients with bone tumors.