

Sample of Proposed Thesis
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Proposal for Investigating Stromal Defects Following Cancer Treatments

The body is made up of many types of cells. Normally, cells grow and divide to produce more cells only when the body needs them. This orderly process helps keep the body healthy. Sometimes, however, cells keep dividing when new cells are not needed. These extra cells form a mass of tissue, called a growth or tumor.

Tumors can be benign or malignant. Benign tumors are not cancerous. They can often be removed and, in most cases, they do not come back. Cells from benign tumors do not spread to other parts of the body. Most important, benign tumors are rarely a threat to life. Malignant tumors are cancerous. Cells in these tumors are abnormal and divide without control or order. They can invade and damage nearby tissues and organs. Also, cancer cells can break away from a malignant tumor and enter the bloodstream or the lymphatic system. That is how cancer spreads from the original cancer site to form new tumors in other organs. The spread of cancer is called metastasis.

Cancer is the second leading cause of death in the United States; leukemia is the most common cancer in children. Leukemia and lymphoma are cancers that arise in blood-forming cells. The abnormal cells circulate in the bloodstream and lymphatic system. They may also infiltrate body organs and form tumors.

Today, bone marrow transplantation (BMT) or peripheral stem cell transplantation (PSCT) may also be used in the treatment of such cancers. The transplant may be autologous (the person's own cells that were saved earlier), allogeneic (cells donated by another person), or syngeneic (cells donated by an identical twin). Both BMT and PSCT provide the patient with healthy stem cells (very immature cells that mature into blood cells). These replace stem cells that have been damaged or destroyed by very high doses of chemotherapy and/or radiation treatment.

Hematopoiesis is the study of the growth and differentiation of blood cells. In adults, blood cell formation occurs within the bone marrow. The bone marrow provides the proper stromal cell microenvironment that allows blood cell formation to occur. In this study, we are interested in determining whether chemotherapy and/or irradiation have an effect on the bone marrow microenvironment, which will affect normal blood cell formation. To accomplish this, we

propose to study the bone marrow stromal microenvironment using an in vitro 'Dexter-type' culture approach.

Bone marrow cells will be obtained from the femurs and tibias of untreated and chemotherapy and/or irradiated treated mice and placed in long-term cultures commonly referred to as 'Dexter-type cultures'. During the initial culture period of three to four weeks, bone marrow cells will form a stromal cell layer on the bottom of the culture vessels, which have the capability to support the growth and differentiation of hematopoietic stem cell. After the stromal layers are formed, we will irradiate the cultures to kill any remaining endogenous hematopoietic cells and reintroduce donor hematopoietic stem cells, which express a marker such as green fluorescent protein or the beta-galactosidase gene. Use of these marked hematopoietic stem cells will allow us to quantitate the maintenance of donor hematopoiesis on top of the various treated stromal layers. If there is a difference in the number and function of these donor stem cells, it will indicate an affect on the ability of the stroma to support hematopoiesis. We will compare normal bone marrow stroma with stroma obtained from mice exposed to various chemotherapies and irradiation for their ability to support hematopoiesis.

It is expected that there will be a visible difference in the number and function of these donor stem cells due to the strength and longevity of irradiation, and different chemotherapies. Results from this investigation may provide evidence of a stromal defect following chemotherapy-related treatments, such as are used in bone marrow transplantation.

References:

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