Cancer immunotherapy using tumor-responsive T Helper 1 cells to inhibit B cell lymphoma development and growth

HYPOTHESIS:
Injection of cloned tumor-responsive T Helper 1 (TH1) cells inhibit tumor development and growth in a mouse model in SJL/J mice in which the majority of untreated mice spontaneously develop B cell lymphomas as they reach 1 year of age. However, the mechanism(s) of tumor inhibition in this model has not been fully characterized. We hypothesize that the in vivo immunotherapeutic effect is mediated by the response of the injected TH1 cells at early stages of malignancy, leading to recruitment and expansion of tumor-specific Cytotoxic T Lymphocytes (CTL) that kill tumor cells before lymphomas become clinically relevant.

PROJECT DESCRIPTION (Include design, methodology, data collection, techniques, data analysis to be employed and evaluation and interpretation methodology)

We have developed cloned TH1 and TH2 cell lines that respond with proliferation and cytokine production to superantigens expressed on the B cell lymphomas that are characteristic of the SJL strain of mouse. In vitro studies have demonstrated that the TH1 (but not TH2) clones promote the development of Cytotoxic T Lymphocytes (CTL) that can kill tumor cells.

These TH1 clones also inhibit tumor growth in vivo. Thus, tumor-injected mice that receive one injection TH1 cells show significantly less tumor growth in a short-term experiment, using a well-established, transplantable lymphoma that grows very aggressively. Moreover, a single injection of tumor-responsive TH1 (but not TH2) cells given to 3 month old SJL mice prevents development of the characteristic primary lymphomas that develop in >95% of aging SJL mice by the time they reach one year of age. Based on our in vitro studies, we feel strongly that following injection into young mice, the tumor-responsive TH1 cells “home” to lymphoid tissues and remain there in a resting state until malignant transformation occurs. Once tumor cells begin to increase in number, the injected TH1 cells then respond to developing tumor cells, as we have shown in our in vitro studies. Once activated, these TH1 cells expand their number, and produce the cytokines necessary to stimulate production of tumor specific CTL that destroy developing tumor cells before they have a chance to become clinical relevant. Thus far, this hypothesis has not yet been tested in vivo. However, we now have the technology to permanently label these TH1 cells (and their progeny) with a marker that allows us to track them, using real-time imaging. Therefore the focus of this project will be to transfect the cloned tumor-responsive TH1 cell line with a vector containing a luciferase imaging marker, inject them into SJL mice, track their patterns of migration and tumor responsiveness, and determine the mechanisms by which this form of adoptive cellular immunotherapy mediates inhibition of tumor growth in vivo.

Methods include:
In vitro procedures: removal of lymphoid tissues and preparation of lymphocyte cell suspensions; short-term lymphocyte cultures; transfection, cloning and maintenance of long-term TH cell lines; assays of lymphocyte function (proliferation, cytokine production, cytotoxicity).
In vivo procedures: maintenance of transplantable tumor cells by serial transplant; tumor growth assays; bio-imaging procedures.
Summer Student Research Program
Project Description

SPONSOR'S MOST RECENT PUBLICATIONS RELEVANT TO THIS RESEARCH:


Li Y, Gasinu S, Ponzio NM, Tsiagbe VK: Dichotomous relationship in regulatory T cell modulation of CD4+ T cell response to endogenous retroviral superantigen vSAg29. (Submitted)

IS THIS PROJECT SUPPORTED BY EXTRAMURAL FUNDS?

Yes ☒ or No ☐

(IF YES, PLEASE SUPPLY THE GRANTING AGENCY'S NAME)

This project is supported by discretionary funds from the laboratories of the participating Principal Investigators

THIS PROJECT IS: ☐ Clinical ☒ Laboratory ☐ Behavioral ☐ Other

THIS PROJECT EMPLOYS RADIOISOTOPES ☒

THIS PROJECT INVOLVES THE USE OF ANIMALS ☒

PENDING ☐ APPROVED ☒ IACUC PROTOCOL #08108D0212
Approved on 2/5/09

THIS PROJECT INVOLVES THE USE OF HUMAN SUBJECTS ☐

PENDING ☐ APPROVED ☐ IRB PROTOCOL # M

WHAT WILL THE STUDENT LEARN FROM THIS EXPERIENCE?

In co-operation with the Principal Investigators of this study, students will participate and gain experience in the experimental design, performance of in vitro and in vivo experiments; collection, analysis, and interpretation of results; and preparation of written or oral presentations related to the results.