LAY TITLE AND ABSTRACT

Modulating Endogenous Nitric Oxide Synthesis for Chemo- and Radio-Sensitization of Tumors.

Chronic inflammation associated with diabetes, obesity, inflammatory bowel disease and certain infectious diseases is also a hallmark of solid tumors and associated with increased risk for several cancer types including colon, pancreatic, lung, endometrial and breast cancer. Chronic inflammatory diseases and solid tumors are both characterized by dysfunctional vasculature as a consequence of an altered nitric oxide synthase activity and generation of highly reactive oxygen/nitrogen free radicals as opposed to stable nitric oxide. These free radicals are used by tumor cells to activate anti-apoptotic, pro-proliferative pathways and enhance DNA damage, both key events of carcinogenesis and tumor progression. Preliminary data demonstrate that the altered nitric oxide synthase activity is due to low amounts of a specific cofactor (tetrahydrobiopterin) and that normal nitric oxide synthase activity can be recovered by dietary means using a precursor of the cofactor, sepiapterin. In the case of carcinogen/inflammatory bowel disease induced colorectal cancer in mice, dietary inclusion of sepiapterin reduces the incidence of colorectal cancer by 80% in mice. Our studies also show that prophylactic treatment with sepiapterin also has some anti-cancer activity against a spontaneous breast carcinoma in mice.

Like most anti-cancer therapies, sepiapterin will probably not be an effective therapy by itself. Thus, the proposed studies will determine whether sepiapterin “normalizes” the dysfunctional vasculature of tumors and by this mechanism enhances anti-tumor drug accumulation in tumors and re-oxygenates tumors thereby radiosensitizing them. For these studies we will use spontaneous tumor models (colorectal and breast cancers) since the animal’s immune system is intact and the tumor vasculature develops with the tumor in contrast to artificial xenograft or orthoptopic tumors in which tumor cells are implanted into the animal. Virginia Commonwealth University and Massey Cancer are fortunate in having state of the art small animal imaging capabilities. The proposed studies will use PET/CT and tomographic photoacoustic imaging to monitor tumor development, blood flow and oxygenation and a CT-based small animal irradiator that using treatment planning similar to what is used in the clinic to deliver tumor-targeted radiation.

Results from these studies will provide the necessary animal preliminary data including imaging necessary for submitting grants to the National Cancer Institute. Furthermore, synthetic tetrahydrobiopterin (Kuvan) used to treat certain forms of phenylketonuria is being investigated clinically to recouple nitric oxide synthases in the treatment inflammatory vascular diseases. Positive conclusions from the proposed experimentation with respect to the efficacy of tetrahydrobiopterin and sepiapterin in controlling breast and colorectal cancer in mice can thus be rapidly translated to the clinic.