

Treatment of Tamoxifen-Resistant Breast Cancer With Vitamin E Succinate

*Primary Investigator: Elizabeth Peralta, M.D.
Funding Agency: SIU Central Research Committee*

Despite advances in chemotherapy and hormonal modulation, one-third of all patients with involved regional lymph nodes die of distant metastases. The selective estrogen receptor inhibitor, tamoxifen (TAM), is an effective adjuvant therapy in estrogen receptor positive (ER+) breast cancer when administered for five years after primary surgery, reducing the risk of relapse by 30 percent. In ER+ metastatic cancer, the initial overall response rate to TAM is 80 percent, but resistance is an inevitable outcome. This project is evaluating the efficacy of vitamin E succinate (VES) in the treatment of tamoxifen-resistant ER+ breast cancer.

Tamoxifen has been associated with higher plasma levels of vascular endothelial growth factor (VEGF) in patients whose breast cancer is in remission. VEGF is one of the most potent inducers of angiogenesis and is a negative prognostic feature when present in breast cancer tumors. Estrogen and TAM each increase production of VEGF in steroid receptor-positive breast cancer cell lines, and it is unknown whether this upregulation of VEGF by tamoxifen might promote tamoxifen-resistant breast cancer recurrence. VES has been shown to inhibit VEGF expression in breast and other tumor cell lines and to inhibit the growth of ER-negative xenografts in mice. Because ER-negative tumors are TAM resistant, the researchers will test whether VES is also effective against ER+ tumors that develop tamoxifen resistance.

Molecular Basis for the Regulation of the Sodium-Calcium Exchanger

*Primary Investigator: Peter Hardwicke
Funding Agency: SIU Central Research Committee*

The level of calcium ions within cells controls many important physiological processes, such as muscle contraction, the transmission of impulses between nerve cells, and the release of histamine in an allergic response. The whole cycle of contraction and relaxation of heart muscle depends on the synchronized entry and removal of calcium. Thus, removal of activating calcium and its restoration to normal levels is of great importance. One way to expel excess activating calcium from the cell is by the sodium-calcium exchanger enzyme present in the outer membrane. It moves calcium out of the cells in exchange for sodium ions.

Dr. Hardwicke's studies are focused on the regulatory loop region of the sodium-calcium exchanger from the adductor muscle of the deep-sea scallop, which contains unusually high levels of exchanger.

Currently, the researchers are working to complete the sequencing of the scallop exchanger. If this can be done, messenger RNA coding for the enzyme can be introduced into oocytes (female reproductive cells) and the whole functional protein incorporated into the membrane so that it can be studied using electrophysiological techniques to determine the effect of phosphorylation on its activity.

Additionally, by labeling the phosphorylated site of an expressed peptide with ³¹P, the researchers will determine the effect of occupation of the calcium regulatory domain by calcium on the phosphorylation domain using

Nuclear Magnetic Resonance and see if this correlates with the previous findings. Using a technique called gel electrophoresis, the researchers discovered that the binding of calcium to the peptide leads to a huge conformational change in the regulatory region. That aspect of the work will be extended using analytical ultracentrifugation.

Immunophenotyping of Cerebrospinal Fluid Lymphocytes in Tourette Syndrome

*Primary Investigator: Michael Pranzatelli, M.D.
Funding Agency: Tourette Syndrome Association Inc.*

"Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections" (PANDAS) is a term that describes children who develop obsessive-compulsive disorder and/or tics, following streptococcal throat infections. Although purported to be autoantibody-mediated, there is a scarcity of immunologic data obtained from the central nervous system in the literature. Immunophenotyping of lymphocytes in the cerebrospinal fluid represents an innovation in the evaluation of centrally mediated pediatric autoimmune disorders. The objectives of this study are to determine the immunophenotype of lymphocytes recruited into the CSF compartment and to evaluate B-cell expansion as a biomarker of disease activity. Finding CSF B-cell expansion in PANDAS and linking it to neurological severity will help substantiate the autoimmune basis of the disorder and provide a possible therapeutic target for innovative therapy.

For more information about these projects, contact the Office of Research and Faculty Affairs at 217-545-7936.