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2001 Program
New Investigator (3-year project)

Project Title: Role of nuclear factor-Kappa B (NF- κ B) and Interleukin-10 in chemotherapy and radioresistance of colorectal cancer

Project Summary: Cancers of the esophagus, stomach and colon are a particularly significant health problem in the aging population. A number of studies have supported an association between cigarette smoking and these cancers. Unfortunately, many gastrointestinal cancers are either inherently resistant to chemotherapy and radiation treatment or they develop resistance during the course of therapy. An important mechanism for resistance to chemotherapy and radiation treatment is inducible resistance, a process whereby exposure of tumor cells to cancer therapy leads to their acquired resistance to cell death. The project proposes that a major mechanism for inducible chemotherapy and radiation resistance is due to increased function of a protein called Nuclear Factor- κ B (NF- κ B). Results from the project laboratory have demonstrated that human colorectal, gastric and esophageal cancer cell lines have a lot of NF- κ B present, and that chemotherapy enhances the NF- κ B activation. Blocking NF- κ B in these cells enhances the toxicity of these chemotherapeutic agents. Results from the studies will be utilized to develop improved methods to treat these tobacco-related cancers by modulating resistance to chemotherapy. This will allow physicians to be more effective to killing these tumors in patients.

Project Successes: The project identified a molecular factor (Nuclear Factor-kappa B) that activates genes in colon, gastric and esophageal cancer cells and protects these cells from the harmful effects of chemotherapy treatment. By inhibiting this molecular factor, these aggressive cancer cells become more sensitive to the effects of chemotherapy. This information can be utilized to design more effective treatment strategies for patients with these cancers. In addition, the chemotherapy dose that is currently utilized can possibly be lowered and have the same effect.

Selected publications from BRP funded research in Peer Reviewed Journals:

Voboril R, **Hochwald SN**, Wessels F, Weberova J, Li J, Brank A, Moldawer LL, Lind S, MacKay SLD. Enhanced chemosensitivity to 5-fluorouracil in colorectal cancer by inhibition of NF-B. *J Surg Res.* 2004;120 (2):178-188.

Camp ER, Li J, Minnich J, Brank A, Moldawer LL, MacKay SLD, **Hochwald SN**. Inducible NF- κ B activation contributes to chemotherapy resistance in gastric cancer. *J Am Coll Surg.* 2004;199(2):249-258.

Hochwald SN, Lind DS, Malaty J, Copeland EM, Moldawer LL, MacKay SLD. Anti-neoplastic therapy in colorectal cancer through proteasome inhibition. *Am Surg.* 2003;69: 15-23.

Selected presentations from BRP funded research:

Minnich DJ., MacKay SLD, Camp ER., Contardo AM., Moldawer LL., **Hochwald, SN**. Enhancement of chemotherapy response in esophageal carcinoma by inhibition of NF- κ B. Presented at the 94th AACR, Washington, DC, 2003.

Camp, ER., MacKay, SLD., Li J., Brank A., Minnich D., Lind DS., Moldawer, LL.,
Hochwald, S.N. PS-341 enhances sensitivity of human gastric cancer to 5-FU and
CPT-11 chemotherapy. Presented at the 94th AACR, Washington, DC, 2003.

New grants based in part on BRP-funded work:

Aventis Pharmaceuticals

Title: Analysis of mechanisms of chemoresistance by gastric cancer to neoadjuvant
irinotecan and docetaxol chemotherapy

Project period: 9/01/01 – 12/01/04

Award amount: \$29,000