madridge CONFERENCES

4th International Cancer Study & Bacteriology Conference

April 3-4, 2019 Philadelphia, USA

Tumor Microenvironment Modulation Enhances Tumor Response to Chemo- and Radio-Therapy using Lonidamine in Cancers

Kavindra Nath[1]*, David S Nelson[1], Jerry D Glickson[1], Ian A Blair[1] and **Dennis B Leeper[2]**
[1]University of Pennsylvania, USA
[2]Thomas Jefferson University, USA

We seek to employ the natural tendency of cancers to convert glucose to lactate as a method for selective intracellular acidification of the tumor, which has been reported to potentiate tumor response to platinum alkylating agents, N-mustards and anthracyclines as well as hyperthermia, radiation therapy and photodynamic therapy; it may also enhance tumor uptake of targeted therapeutics. As a consequence of high levels of aerobic glycolysis, tumors exhibit an acidic extracellular pH (pHe) and a neutral to alkaline intracellular pH (pHi) leading to an acid-outside/neutral to mildly alkaline inside plasmalemmal pH gradient. This gradient also impacts tumor response to certain chemotherapeutic modalities. Manipulation of pHe and/or pHi of tumors have considerable impact on tumor growth and metastasis as well as response to therapy. Extracellular tumor acidification has been modified by administering sodium bicarbonate in order to increase the pHe and thereby reduce tumor invasiveness and facilitate uptake of weakly basic chemotherapeutic drugs. In contrast, our aim was to decrease the pHi in order to increase the intracellular activity of chemotherapeutic agents. We accomplished this by administering lonidamine (LND, 100 mg/kg, intraperitoneal), an inhibitor of the monocarboxylate transporter (MCT), mitochondrial pyruvate carrier and complex II of electron transport chain that blocks cellular export of lactic acid and also inhibits transport of pyruvate into mitochondria, thereby inhibiting tumor energy production. LND sensitizes tumors to radiation therapy by increased tumor oxygenation and decreased ATP levels and decreased levels of glutathione. Other MCT inhibitors such as AZD3965 manufactured by AstraZeneca, alone or in combination with complex I inhibitors (metformin, phenformin) may exhibit similar properties to LND in modifying tumor pHi and bioenergetics. These agents may therefore, play an important role in modifying the tumor microenvironment to make more susceptible to certain classes of chemotherapeutic agents and to radiation therapy.

Biography:

Dr. Kavindra Nath is a Research Assistant Professor of Radiology at the University of Pennsylvania, Perelman School of Medicine. He did Ph.D. in Magnetic Resonance Imaging and Spectroscopy (MRI/MRS) from a premier medical institute in India. In Ph.D. he studied the role of MRI/MRS techniques in the differential diagnosis of cystic intracranial mass lesions in patients. His current research at the University of Pennsylvania in Department of Radiology is to utilize multi-nuclear (^{1}H, ^{31}P, ^{13}C) MRS *in vitro* and *in vivo* and other techniques such as mass spectrometry in order to delineate the mode of action of lonidamine and various other metabolic modulators, which distinguishes normal cells from malignant cells and potentiates the activities of various chemotherapeutic drugs, radiation therapy and hyperthermia in a variety of human cancers. He has published 36 peer reviewed research papers in reputed journals and has been serving as an editorial board member of many reputed journals. He has delivered many invited talks at various conferences and institutions.