

MONTI HUGHES-1: Optimizing BNCT for Different Pathologies: Translational In Vivo Studies Searching to Bridge The Gap Between Research and Clinical Application

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BNCT clinical trials for several pathologies have shown a significant therapeutic advantage, associated to an improvement in patient quality of life and prolonged survival. Nevertheless, there is room for improvement in terms of enhancing BNCT therapeutic efficacy and minimizing the associated toxic side-effects. Translational radiobiological studies in appropriate in vivo experimental models are pivotal to the advancement of BNCT. A significant part of our translational research efforts have been focused on exploring new applications of BNCT and optimizing BNCT for different pathologies, for varying degrees of disease progression and for different clinical conditions of the patient. Since 1998, our group has explored novel boron compounds and studied different delivery strategies of the boron compounds that have been/are used in humans, employing a bench to bedside approach that bridges the gap between research and clinical application. All these studies were performed in collaboration with several international and national groups. Some examples of our studies are: 1) Combined administration of BPA and GB-10 to improve tumor boron targeting homogeneity in the hamster cheek pouch oral cancer model, in a colon carcinoma liver metastases model in BDIX rats and in a diffuse lung metastases model in BDIX rats; 2) Biodistribution studies of BSH and BPA administered jointly in the oral cancer model; 3) Normalization of aberrant tumor blood vessels to improve boron delivery in the oral cancer model; 4) Sequential BNCT (BPA/BNCT followed by GB-10/BNCT with a 24-48 h interval) in the oral cancer model to optimize therapeutic efficacy and minimize mucositis in the dose-limiting precancerous tissue in the case of patients requiring abbreviated treatment; 5) Electroporation to improve the gross boron uptake and microdistribution delivered by GB-10 in the oral cancer model; 6) Double applications of BNCT with 4-6 weeks interval to optimize therapeutic efficacy, reduce toxicity in terms of mucositis and inhibit the development of second primary tumors from precancerous tissue in the oral cancer model for the case of patients that do not require abbreviated treatment; 7) The study of different compounds combined with BNCT, such as fucoidan (an algae biopolymer), aimed at reducing BNCT toxicity and/or enhancing BNCT therapeutic effect on tumors in hamster and BDIX rats; 8) Assessment of the therapeutic efficacy and potential toxicity of BNCT in the liver metastases and diffuse lung metastases models in BDIX rats; 9) Local administration of GB-10 or BPA for effective low dose Boron Neutron Capture Synovectomy (BNCS) for the treatment of Rheumatoid Arthritis in a model of antigen-induced arthritis in rabbits; 10) BNCT-induced local and abscopal effect in an ectopic model of colon carcinoma in BDIX rats; 11) The benefit of combining BNCT with immunotherapy on local and abscopal effects. All these studies led to our ongoing clinical-veterinary BNCT studies at the RA-1 and RA-6 nuclear reactors, for cats and dogs with spontaneous head and neck cancer with no other therapeutic option. BNCT improved the clinical condition of the veterinary patients, prolonged survival with good quality of life and partially controlled tumors with only slight-moderate and reversible associated toxicity. The knowledge gained from our radiobiological studies would contribute to design safe and effective clinical BNCT protocols.