

2016 Research Support Grants (RSG)

University of Washington

Adjunctive pentoxifylline and tocopherol (PENTO) in the treatment of medication-related osteonecrosis of the jaw (MRONJ): a prospective, randomized controlled trial to evaluate a novel non-operative treatment.

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Summary: Medication-related osteonecrosis of the jaws (MRONJ) is an uncommon, but serious, complication of anti-resorptive and anti-angiogenic medications in the management of osteoporosis and to limit skeletally related events in cancer patients. Oral and maxillofacial surgeons diagnose and manage MRONJ. We continue to find more medications that have potential to lead to osteonecrosis of the jaw and the associated morbidity experienced by these patients. There are few non-operative treatment options for patients with MRONJ. The treatment objectives for patients with MRONJ as defined by the AAOMS Position Paper are to: 1) eliminate pain, 2) control infection of the soft and hard tissue, and 3) minimize progression or occurrence of bone necrosis. The standard of care (SOC) of non-operative management of MRONJ is limited to topical chlorhexidine mouth rinse, systemic antibiotics and analgesics. Non-operative SOC may be complemented by operative treatment ranging from local debridement to resection with or without free flap reconstruction. The AAOMS position paper calls for controlled trials, to understand better the efficacy of non-operative treatment strategies to meet the treatment objectives listed above. To that end, we propose to evaluate the efficacy of pentoxifylline and tocopherol (PENTO) in the non-operative management of MRONJ. Pentoxifylline is commonly used for peripheral artery disease. It is proven to improve peripheral blood flow, flexibility of red blood cell membranes, microcirculation, and tissue oxygenation and reduces viscosity of blood. Tocopherol (vitamin E) impairs tissue fibrosis and is a potent oxygen radical scavenger that may reduce damage caused by free radicals impacting necrosis. PENTO shows promise as an effective treatment in improving the prognosis of osteoradionecrosis of the jaw (ORN) (Delanian, 2011). Some authors have successfully applied PENTO regimens to all stages of MRONJ (Epstein, 2010 and Magremanne, 2014). Although these results are promising, the present evidence for effective PENTO treatment is anecdotal. Larger, prospective, randomized clinical trials are needed to evaluate effectiveness. Our clinical trial is to investigate PENTO as a non-operative treatment strategy for the treatment of MRONJ.

University of Pennsylvania

Defining mechanical injury, hypoxia, and disease progression in TMJ OA and Pain

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Summary: Temporomandibular joint disorder and pain remains the second most common musculoskeletal pain condition behind lower back pain with fifteen percent of this patient population progressing to develop chronic pain. Identifying this recalcitrant subgroup remains a difficult clinical problem requiring a better understanding of the pathophysiology in order to develop clinically meaningful biomarkers of disease progression. This research proposal lays the foundation to evaluate biomarkers of chronic TMJ disease and pain, as well as to define the early cellular mechanisms in the joint and nervous system associated with the development and maintenance of chronic orofacial pain. Recent evidence supports the role of mechanical overload, hypoxia and low-grade inflammation in TMJ OA as primary mechanisms of progressive dysfunction and pain. Hypoxia inducible factor (HIFs), when upregulated, have been recently demonstrated to contribute to joint degeneration in osteoarthritis of other joints and remains an exciting potential early marker in TMJ disease. We recently developed a mechanical model of TMJ injury in the rat that allows for tunable outcomes of acute or chronic pain. In our chronic pain model, we have demonstrated the upregulation of inflammatory markers (TNF α) matrix metalloproteinases (MMP-13), and HIF2 α , in our model that parallels what is observed in human disease. We propose to investigate the role of HIF 2 α HIF2 is necessary in the early initiation of progressive joint degeneration, and persistent pain in TMJ OA.

University of Pennsylvania

Stromal cell-derived IL-6 promotes epithelial tumor stem-like cell generation by inducing epithelial-mesenchymal transition in ameloblastoma.

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Summary: Ameloblastoma is a benign but locally aggressive tumor with a high tendency to recur and consists of proliferating odontogenic epithelium among a midst of fibrous stroma. Anatomically, ameloblastoma occur more frequently in the mandible, mainly in the third molar region. The solid/multicystic ameloblastoma is the most common and aggressive type, comprising 91% of clinical cases. Currently, surgical resection is the preferred treatment, which causes severe bone defect and morbidity to the craniofacial complex. It has been postulated that ameloblastoma may have originated from residual epithelium of the tooth germ, or epithelium of odontogenic cysts, and epithelium of the enamel organ; however, the pathophysiology of this aggressive benign tumor remains largely unknown. Cancer stem cells (CSCs) constitute a unique subpopulation of cells within a tumor that may play a critical role in recurrence, relapse and metastasis of malignancies. Epithelial-to-mesenchymal transition (EMT) is a fundamental process during development in multicellular organisms and also constitutes a crucial step in the aggressive invasion and metastatic spread of a variety of epithelial tumors. This process is dynamic, reversible and bidirectional (EMT vs. MET), thus contributing to the plastic state of tumor cells or the acquisition of tumor stem-like cell properties. Emerging evidence suggests that the bidirectional EMT process and tumor stem-like cell properties are tightly regulated by various extrinsic signals from the tumor environment, where stromal cells in tumors predominate. However, little is known about the role of EMT process and tumor stem-like stem cells in epithelial benign tumors, including ameloblastoma. In our preliminary study, we were able to isolate and characterize epithelial and stromal cells from human follicular ameloblastoma. These populations of epithelial cells displayed a panel of stem cell-related genes both in vivo and in vitro, which might have correlated with the expression of EMT markers and abundant expression of IL-6 in the surrounding stromal cells. In the present study, we will delineate the role of stromal cell-derived IL-6 in the regulation of EMT process and acquisition of stem-like cell properties in ameloblastoma epithelial cells and the underlying signaling mechanisms. The anticipated findings will substantially expand

current knowledge regarding the EMT process and tumor stem-like formation in the pathogenesis of benign odontogenic tumors, thus potentially contribute to novel immunotherapeutic approaches for the treatment of malignant and benign tumors that are currently resistant to conventional therapies.