THE HARTWELL FOUNDATION

2010 Individual Biomedical Research Award

Review of Proposed Research

Investigator: **Nan E. Hatch, DMD, Ph.D.**
Assistant Professor
Department of Orthodontics and Pediatric Dentistry

Institution: **The University of Michigan**

Proposal: **In Vivo Manipulation of Tissue Nonspecific Alkaline Phophatase Enzyme Expression: A Biomedical Strategy for the Prevention and Treatment of Craniosynostosis**

Craniosynostosis is a debilitating pediatric condition in which skull bones prematurely fuse together. The prevalence of craniosynostosis is high; approximately 1 in 2500 live births. Current treatment is limited to surgery, with medical and social support. Untreated craniosynostosis can cause blindness, seizures and death. It has been known for over a decade that craniosynostosis is associated with mutations in the genes for fibroblast growth factor receptors (FGFR), yet the biologic mechanism by which these mutations (changes in the DNA sequence) lead to this abnormality is unknown. Even with an appropriately early and accurate diagnosis, craniosynostosis carries high morbidity. Patients and their families carry substantial financial, medical and psychological burdens because today the only available treatment is surgery and many patients require multiple surgeries throughout childhood for relief of high intracranial pressure and normalization of skull and facial shapes. Based upon her innovative recognition of the relationship between FGFR mutations, diminished tissue non-specific alkaline phosphatase (TNAP) enzyme and craniosynostosis, Nan hypothesizes that low TNAP enzyme levels leads to abnormal mineralization of skull bones and sutures (the non-mineralized fibrous tissue present between adjacent skull bones), and therefore to craniosynostosis. Her preliminary data (2009) suggests that TNAP enzyme levels are low in skull tissues of mice that carry the most common human craniosynostosis-associated mutation in FGFR2, which correlates well with the observation that craniosynostosis also occurs at high rates in infants with mutations in the gene for TNAP. Nan proposes to test her hypothesis that local delivery of TNAP enzyme will prevent craniosynostosis in mice that carry the most common human craniosynostosis-associated mutation in FGFR2. If she is successful in finding that TNAP is essential for the prevention of craniosynostosis, medical approaches currently in use for the treatment of patients with insufficient TNAP (hypophosphatasia, the extracellular accumulation of inorganic pyrophosphate that inhibits skeletal mineralization) may also prove applicable for the treatment of patients with craniosynostosis. Successfully demonstrating the role of decreased TNAP in the pathogenesis of craniosynostosis will thus enable the clinical translation of the first and only nonsurgical treatment option for infants and children with craniosynostosis, representing a dramatic improvement in their quality of life.