Principal Investigator	Nan Hatch, DMD PhD
Co-Investigator	
Secondary Investigators	
Award Type	AAOF Orthodontic Faculty Development Award (originally submitted and accepted by PARC as an AAOF Post-doctoral Fellowship Award)
Project Title	TM Graber Teaching Fellowship Award
Project Year	2009-2010
Institution	University of Michigan
Summary/Abstract (250 words maximum)	The research aspect of this proposal seeks to investigate a novel biologic mechanism underlying the pathogenesis of craniosynostosis. Craniosynostosis is the debilitating clinical condition of premature cranial suture fusion. That syndromic craniosynostosis is associated with activating mutations in fibroblast growth factor receptors (FGFR's) and the transcription factor, Msx2, has been known for over a decade, yet the precise biologic mechanism by which these mutations result in the disease phenotype has yet to be elucidated. Results from the proposed research will provide strong rationale for the development of biologic therapeutics for treatment of patients with this condition. **SPECIFIC AIM: Investigate PC-1 as a key mediator of craniosynostosis.** **Rationale:** We find that FGF2 induces expression of the pyrophosphate generating enzyme, PC-1, and that this is mediated by the transcription factor Msx2. These findings are highly significant. PC-1 generated pyrophosphate regulates bone and soft tissue mineralization. Because FGF receptor and Msx2 activity induce expression of PC-1, because activating mutations in FGF receptors and Msx2 are associated with craniosynostosis, and because craniosynostosis is also known to occur in patients with high pyrophosphate levels due to mutations in alkaline phosphatase, the induction of PC-1 by FGF signaling and Msx2 activity could account for the aberrant calcification seen in the craniosynostosis phenotype. *We hypothesize that increased PC-1 expression results in the craniosynostosis phenotype of Crouzon syndrome*. Accordingly, I propose to cross the $FGFR2^{C342Y}$ mouse model of Crouzon syndrome with the PC-1 null mouse to directly investigate PC-1 as a key mediator of craniosynostosis *in vivo*.

Were the original specific aims of the proposal realized?	The research goals of this proposal are in the process of being met. Substantial data has been generated, presented and utilized for grant application. One manuscript has been submitted for publication and is under review. A second manuscript is in progress. Most significantly, an R03 research application has been written and submitted to the National Institute of Dental and Craniofacial Research (NIDCR). This application has been reviewed and received an "outstanding" impact/priority score of 20 (this score corresponds to the NIH descriptor "extremely strong with negligible weaknesses"). Funding decisions will be made in July of 2010. If the grant is not funded, it will be rewritten and resubmitted. My professional development during this period has been strong. I am now an elected GLAO representative to the Council on Scientific Affairs (COSA) for the AAO and a member of the GLAO board. I continue to review manuscripts for the AJODO and several other biomedical journals. I am also an organizing board member of COAST (Conference on Orthodontic Advances in Science and Technology) and an elected director for the Craniofacial Biology Group of IADR (International Association of Dental Research). During this fellowship period I have also continued to develop and teach didactic curriculum on the biology of orthodontic tooth movement, orthopedic growth modification and orthodontic associated root resorption. This course has been highly received by the orthodontic residents and will be expanded in the future. I have also developed an Introduction to Research Topics course, which is given to the orthodontic residents in their first fall semester. This course introduces the residents to potential research mentors, and provides guidelines and instruction for developing a Master of Science research project. This course is currently being expanded to include project presentations by second year orthodontic residents, to facilitate consistent and early feedback for the residents. I am also an active member on several Orthodontic Resident Master of Science Thesis Committees, and am currently the committee chair for two resident projects. In addition, I have successfully negotiated a contract to work with Amgen (independent biomedical company) for collaborative work and access to recombinant biologic mediators for enhancement of orthodontic tooth movement, retention and anchorage. While translation of this work into clinical practice will take time, we should be able to determine the clinical utility of these recombinant proteins through a series of orthodontic resident projects. These mediators are also actively being pursued by others for the treatment of osteopenia and osteoporosis, which should ultimately ease translation into the clinic.
Were the results published? If not,	Yan L, Kim S and **Hatch** NE (2010). *FGF2 promotes Msx2 stimulated PC-1 expression via Frs2/MAPK signaling*. J Cell Biochem, in review.

are there plans to publish? If not, why not?	Ge C, Xiao G, Jiang D, Yang Q, **Hatch** NE, Franceschi RT (2009). *Identification and functional characterization of extracellular-regulated kinase/MAPK phosphorylation sites in the Runx2 transcription factor.* J Biol Chem, 284(47):32533-43. **Hatch** N, Yan L and Franceschi RT (2009). FGF2 stimulated expression of the pyrophosphate generating enzyme, PC-1, is mediated by Runx2. J Bone Min Res, 24(4):652-62.
Have the results of the proposal been presented? If so, when and where? If not, are there plans to do so? If not, why not?	**Hatch**, N (2010). *The Biology of Orthodontic Tooth Movement: Current Concepts and Applications to Clinical Practice*. Oral presentation, Annual Session of the American Association of Orthodontists, Washington, D.C. **Hatch**, N. (2010) *Fibroblast Growth Factor (FGF) Induced Pre-Osteoblast Expression of the Pyrophosphate Generating Enzyme, PC-1: Implications for Craniosynostosis?* Oral Presentation, 25th Annual Conference of ASBMR 's Advances in Mineral Metabolism, Snowmass, CO. **Hatch**, N. (2010) *Current concepts in the biology of orthodontic tooth movement: Translation from the bench to the clinic.* Oral presentation, Moyers Symposium, Ann Arbor, MI. **Hatch**, N. (2009*).* Invited seminar presentation to OSU orthodontic residents on, *"The biology of orthodontic tooth movement"*, Ohio State University, Department of Orthodontics, Columbus, OH. **Hatch**, N. (2009). Invited oral presentation to OSU bone research group on *"Mediators of FGF signaling effects on bone mineralization and craniofacial skeletal development"*, Ohio State University, Columbus, OH. **Hatch** N (2009). *Current Concepts in the Biology of Tooth movement: Translation from Bench to Clinic*. Oral presentation, Annual Session of the American Association of Orthodontists, Boston, MA.
Awards	2010 John Haddad Young Investigator Award Advances in Mineral Metabolism American Society for Bone and Mineral Research