AAO Foundation Award Final Report

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Award Type	Faculty Development Fellowship Award
Project Title	ROLE OF OSTEOBLASTIC HIF SIGNALING AS AN UPSTREAM FACTOR IN OSTEOCLAST MATURATION-ACTIVATION
Project Year	2007
Institution	University of Oklahoma
Summary/Abstract (250 word maximum)	**Background:** There has been considerable debate as to the origin of osteoclasts (OC) involved in bone remodeling during orthodontic tooth movement with a general consensus that OC come from the bone marrow. OC have been cultured from monocytes in the presence of RANKL, a soluble ligand released by osteoblasts (OB). We hypothesized that osteoclastic differentiation from monocytes during tooth movement is initiated by hypoxia after occlusion of the blood vessels. **Objective:** The objective of this project was to demonstrate upregulation of OC growth factors released from OB and subsequent conversion of peripheral blood monocytes (PBMNC) into functional OC. **Material & Methods:** Human PBMNC were co-cultured with/without osteoblasts and either subjected to 2.5% hypoxia or normoxic conditions for 14 days. Supernatant was collected and levels of hypoxia inducible factor (HIF), vascular endothelial growth factor (VEGF) and RANKL were measured. Development of OC was measured using TRAP procedure. **Results:** We observed upregulation of HIF, VEGF and RANKL under hypoxia but not in normoxic conditions. OC were observed in the hypoxic conditions only and when co-cultured with osteoblasts. OC development was correlated to VEGF and RANKL. **Conclusion:** Hypoxia can trigger the differentiation of PBMNC into osteoclasts in the presence of osteoblasts.
Were the original, specific aims of the proposal realized?	The project was designed to address two specific aims: 1. Do osteoblasts (OB) respond to hypoxia by induction of HIF signaling? 2. Does hypoxia result in the production of remodeling OC? Both aims were realized and much more than anticipated, and is the basis of our continued research in that field.
Were the results	Manuscript is under review.

published? If not, are there plans to publish? If not, why not?	
Have the results of this proposal been presented? If so, when and where? If not, are there plans to do so? If not, why not?	Part of the results generated from this project have been presented to NIH for the Junior Investigator Award funding. Reviewers were interested in the project, and suggested that the best avenue for funding would be an RO1. We will be submitting an RO1 proposal to the NIH for the next round of funding. Also, we will be submitting a proposal to the Reynolds Oklahoma Foundation for Research (ROCA) in September for 1-2 year ROCA funding. Results of this research will be competitively presented at the next AAO meeting and we have already responded to a call for proposals.