AAO Foundation Award Final Report

Principal Investigator	Chin-Yu Lin, DDS, MS, MSD, PhD
Co-Investigator	
Secondary Investigators	
Award Type	Post-doctoral Fellowship Award
Project Title	The molecular signals in the osteoclast recruitment and differentiation during tooth eruption using cherubism model
Project Year	2007-2008
Institution	Harvard School of Dental Medicine
Summary/Abstract (250 word maximum)	Cherubism, caused by mutations on SH3BP2, is characterized by multi-cystic bony lesions of jaw bones in childhood and adolescence. It is a TNF-α dependent hematopoietic disorder with aberrant myeloid cells (macrophage and osteoclasts). Temporal and spatial manifestations of cherubism suggest a role of dental follicles in the pathogenesis. M-CSF and MCP-1 have been indicated to play a crucial role in the osteoclast recruitment by dental follicles during tooth eruption. Dental follicles from cherubism mutants and wild type mice secreted MCP-1, but not M-CSF. Addition of TNF-α increased the secretion of MCP-1 with no M-CSF being detected. Cross-breeding of cherubism mice with MCP-1-deficient mice showed the similar massive infiltration of macrophages into jaw bone and other skeletal elements and internal organs with abnormal bone resorption as cherubism mice. The migration assay of myeloid cells to dental follicles showed that dental follicles attracted myeloid cells and TNF-α increased the attraction. However, the depletion of MCP-1 did not change the migration of myeloid cells to dental follicles. These results suggested that M-CSF and MCP-1 were not crucial signals from dental follicles in the osteoclast recruitment. To further investigate the signals in aberrant osteoclast differentiation in cherubism, we cross-bred cherubism mutants with NFATc1, a transcriptional factor in terminally differentiating osteoclasts, conditional knock-out mice. The results showed that deletion of NFATc1 protect bone loss from cherubism. This indicated that cherubism patients who suffer from jaw bone loss may benefit from the treatment with cyclosporine A or FK506 that inhibit NFAT activation.
Were the original, specific aims of the	We finished specific aim in the osteoclast recruitment. For the specific aim in the osteoclast differentiation, we made some changes

proposal realized?	because the acquired OPG deficient mice did to breed. Therefore, the aim was changed to the signaling mechanisms of osteoclast differentiation as stated in the summary. With the acquiring of OPG-deficient embryos lately, we will resume the aim.
Were the results published? If not, are there plans to publish? If not, why not?	The current results have not been published. We plan to publish the data with more mechanisms deciphered.
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?	The current results have not been present. We plan to present the data in the annual meeting of the Harvard Society for the Advancement of Orthodontics on November 1st of 2008.