AAO Foundation Award Final Report

Principal Investigator	Peter T. Gakunga, BBS, MS, PhD
Co-Investigator	
Secondary Investigators	
Award Type	Orthodontic Faculty Development Fellowship Michael Matlof Memorial Teaching Fellowship Award
Project Title	Molecular Mechanisms Controlling Growth in the Cranial Base Synchondroses
Project Year	2004
Institution	University of Texas Health Science Center at San Antonio
Summary/Abstract	The incidence of craniofacial growth abnormalities is 1:1000 of all live births. The clinical burden on these patients ranges from psycho-social isolation, to compromised neural, visual and psycho-social development. The long term goal of this project is to understand the molecular mechanisms regulating growth in the cranial base synchondroses. An understanding of cranial base chondrocyte differentiation and maturation is critical for deciphering both normal and abnormal craniofacial growth. We hypothesize that modulation of endogenous HA by TGF-β regulates chondrocyte hypertrophy in the cranial base synchondroses. The study uses coordinated biochemical, molecular, and organ culture approaches to test this hypothesis. The studies characterize the spatial-temporal expression patterns of hyaluronan, CD44, and TGF-β receptors by the cranial base chondrocytes as well as their extracellular milieu. The study also determines the physiological role of secreted members of the TGF-β family that modulate CD44 and hyaluronan expression in cranial base chondrocytes. Hyaluronan and CD44 antagonists as well as TGF-β1 are incorporated into a novel cranial base organ culture system to assess the effects of attenuating CD44- hyaluronan expression and interaction on the synchondrosal growth. The results demonstrate that: • Hyaluronan-mediated mechanisms play an important role in controlling normal lacunae expansion in the zone of hypertrophy in cranial base synchondroses. The hyaluronan-mediated mechanisms are mediated through cell surface receptors.

	• TGF-β1 inhibits longitudinal cranial base growth. Possibly through interactions with HA-mediated mechanisms • Together these results provide strong evidence that the cranial base organ culture system is viable for the testing of our hypothesis. This technique will be effective in further experiments designed to continue elucidating the mechanisms controlling growth in the cranial base synchondroses The continuation of this work will provide valuable information on the molecular pathology of craniofacial dysmorphology, as well as provide pointers towards novel diagnostic and treatment strategies.