Type of Award: Postdoctoral Fellowship Award

Name of Principal Investigator: Siddharth R. Vora

Title of Project: THE RELATIONSHIP OF CRANIOFACIAL SYNCHONDROSES / SUTURES TO MIDFACE GROWTH AND HYPOPLASIA

Period of AAOF Support: July 2015 to June 2016

Amount of Funding: $50,000

Summary/Abstract (250 word maximum)

Despite the widespread prevalence and challenges in treatment of midface hypoplasia (MFH), not much is known about its pathogenesis. This study aimed to elucidate the role of specific cranial base synchondroses in the pathogenesis of MFH by phenotypic characterization of mutant mouse strains that display combined defects in cranial base, vault and facial growth. Investigation of the spontaneously arisen *shsn* and *snol* mutant mouse strains revealed variable severity of MFH ranging from mild to severe with anterior crossbites. Compared to wild-type control animals, premature closure of the intersphenoidal synchondroses (ISS) and variable closure of the sphenoocciptial synchondroses (SOS) was also observed. In addition, two Apert mouse strains in which the activating Fgfr2 S252W mutation is conditionally expressed using different driver lines, were also analyzed. When this mutation is driven by *Wnt1Cre*, severe MFH with cranial doming and frontal bone bossing was found. Cranial base dimensions were severely deficient and consistent premature closure of the ISS and variable closure of the SOS was observed. Premature fusion of cranial and facial sutures was also found. Cellular histological analyses suggest primary defects in the resting zone of the chondrocytes. In contrast, when this mutation was expressed driven by *Osx-Cre,* premature closure of the synchondroses was not observed. However some facial and cranial vault sutures fused early and mild MFH with incisor crossbites was present. Together, these mouse models strengthen the hypothesis that cranial base growth defect can affect growth and projection of the midface and present good models wherein further studies on MFH pathogenesis can be performed.

Response to the following questions:

1. **Were the original, specific aims of the proposal realized?**
   The specific aims of the proposed project have been partly realized. With respect to Aim 1, phenotypic comparisons of the two strains (*shsn* and *snol*) have been performed while gene mutation identification of only the *shsn* strain has proven successful. With respect to Aim 2, analysis of the Wnt1-Cre, $Fgfr2^{NC\text{-}S252W/+}$ and Osx-Cre, $Fgfr2^{NC\text{-}S252W/+}$ has been performed, however work on the Aggc-Cre, $Fgfr2^{NC\text{-}S252W/+}$ has not been initiated. As I transitioned into a full-time faculty position during the course of the award, an independent line of investigation was commenced (and is ongoing). Maintaining the original questions in the proposed study, we investigated the relationship of the midface to cranial base synchondrosis utilizing human data. Closure status of the SOS was analyzed (using a 6 point grading scale) and correlated to

midfacial projection measurements, made on CBCT scans of non-syndromic patients aged 5.5-10.5 years (n=94). This work has generated intriguing preliminary data suggesting a trend that children in whom the SOS began fusion earlier, display mildly retrusive maxilla. More studies with a larger sample size are need to further assess this trend, and are being planned.

2. **Were the results published**? Part of the work performed during the PFA have been published. Additional publications are being prepared and will be submitted once completed.
   a. If so, cite reference/s for publication/s including titles, dates, author or co-authors, journal, issue and page numbers
   1. Vora S.R. "*Mouse models for the study of cranial base growth and anomalies"*. Orthodontics and Craniofacial Research. 2016 (Accepted)
   2. Fraizer-Bowers S. and Vora S.R. "*Genetic disorders of dental development: tales from the bony crypt*". Current Osteoporosis Reports. 2016 (Submitted)
   3. Vora S.R., Camci ED, Cox T.C.. "*Postnatal Ontogeny of the Cranial Base and Craniofacial Skeleton in C57BL/6J mice: A Reference Standard for Quantitative analysis*". *Frontiers in Physiology* 6:417.doi:10.3389/fphys. 2015

   b. Was AAOF support acknowledged?
   Yes, AAOF support was acknowledged.

3. **Have the results of this proposal been presented?**
   Work done on this project has been presented at the meetings noted below.
   a. If so, list titles, author or co-authors of these presentation/s, year and locations
   1. "*Novel mouse models of midface hypoplasia display cranial base growth defects"*. International Association of Dental Research (IADR) – Boston, MA
   2. *"Mouse models for the study of cranial base growth and anomalies"*. Consortium for Orthodontic Advances in Science and Technology (COAST), 2016, West-Palm Beach, FL

   b. Was AAOF support acknowledged?
   Yes, AAOF support was acknowledged.

4. **To what extent have you used, or how do you intend to use, AAOF funding to further your career?**
   Funding from the AAOF in the past years has enabled me to pursue an academic career. In a financially challenging research environment, this award afforded me the ability to follow an organized period of research development during my post-doc. I recently began a full-time academic position at UBC, and having been funded by the AAOF certainly bolstered my CV, presenting me as an attractive and viable faculty candidate. Continued support from the AAOF is not only encouraging but more importantly, enabling. I believe it will be crucial to my future goals of obtaining independent research funding. I thank the foundation, the PARC committee and all of its champions and hope to continue a positive relationship with this organization.