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Title of the Project: The mechanistic role of NELL-1 in cranioynostosis

Institute: UCLA School of Dentistry

Summary:

Craniosynostosis (CS), the premature closure of cranial sutures, is the on of the most common human congenital craniofacial deformity. Currently, fibroblast growth factor receptor (FGFR) mutations are the most highly characterized genetic defects in CS. However, FGFR mutations primarily apply to familial CS cases, which account for only 2-8% of the entire CS spectrum. Moreover, most transgenic mice models of CS with either FGF or FGFR mutations exhibit *non*-congenital CS (i.e., late developing CS) and extra-cranial deformities that are not observed in the majority of CS patients. Here, we report the recreation of congenital human CS phenotypes without extra-cranial deformities in transgenic mice with *NELL-1* over-expression. Previously, we had demonstrated specific *NELL-1* over-expression in premature closing sutures of unilateral coronal CS (UCS) patients, a prevalent form of non-familial and non-syndromic CS. CS phenotypes in *NELL-1* transgenic mice ranged from compound synostoses such as craniotelencephalic dysplasia to simple synostoses. Histologically, *NELL-1* CS phenotypes exhibited disorganized suture formation, closure, and increased apoptosis along fusing calvarial edges. *In vitro*, *NELL-1* over-expression promoted calvarial osteoblast differentiation, mineralization, and apoptosis with concomitantly altered expression of bone differentiation markers, growth factors, and apoptosis-related genes. Physiological *NELL-1* expression was primarily restricted to calvarial bone. We conclude that *NELL-1* may represent a new molecule with specific functions in normal suture biology and suture pathology—and that *NELL-1* over-expression may disrupt normal calvarial osteoblast differentiation and apoptosis pathways to induce premature suture closure.