"Identification of Subclasses of Cerebellar Granule Neuron Progenitor Cells, and their Potential to form Pediatric Brain Tumors"

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Abstract: Medulloblastoma, the most common malignant nervous system tumor in childhood is thought to arise in precursors of the cerebellar granule neuron (GCPs). The remarkable number of cerebellar granule cells, which outnumber the neurons of the cerebrum, increase dramatically during vertebrate evolution, by a feedback loop between granule neurons and the other principal cerebellar neuron, Purkinje cells. Purkinje cells provide a principal GCP mitogen, SHH, and Wnt3, which blocks SHH growth stimulation and slows medulloblastoma growth. We will also examine two other pathways - PP2a, a regulator of N-myc and inhibitor of growth factor-induced kinases, and Rnd3, a constitutively active RhoA that transforms non-neuronal cells by a mechanism that by-passes known cell cycle "check-points". We plan to (1) define the role of Rnd3 and PP2a in GCP differentiation and tumorigenesis, and (2) assay the influence of SHH, Wnt3, PP2a and Rnd3 on neonatal, juvenile and adult granule cell proliferation and tumorigenesis using a novel BAC-array gene expression system. In the long term, we will use this general strategy to provide insight on the emergence of different classes of medulloblastomas in subsets of cerebellar granule neurons.