The Small GTPase ARF6 is an Actionable Node in Uveal Melanoma
Research Summary by Dean Y. Li, M.D., PhD, University of Utah

The MRF is proud to support the research being conducted at Dr. Li's lab through our Career Development Award. Dr. Li presented this research at the 2016 Society for Melanoma Research Congress CURE OM Scientific Meeting and offered the following summary.

Within cancer cells there is a command central from which all orders for growth and invasion originate. Driver mutations are the equivalent of the commander in chief. In most uveal melanoma tumors, the initial signal for growth emanates from either one of two related commanders: the oncogenes GNAQ or GNA11. Their orders are executed by a hierarchy of subordinate officers, proteins such as PLC, YAP and β-catenin, and numerous downstream messengers and troops.

Successful military operations must have a reliable and efficient means of transporting supplies, equipment and personnel to implement their plan. We found that the protein ARF6 coordinates the transportation of the commander GNAQ to cytoplasmic vesicles, a strategic intracellular rendezvous site, where GNAQ issues orders to its immediate subordinates (PLC, YAP, β-catenin) to promote growth of the cancer.

The role of ARF6 in uveal melanoma is similar to that of a train conductor, ensuring trafficking of GNAQ and other key proteins to the appropriate destination within the cell. Without this transport step, GNAQ is ineffective in driving growth. In fact, pharmacologic blockade of ARF6 prevents this transport process, the transmission of the command signal from GNAQ and the growth of the tumors in mouse models of uveal melanoma. We have identified the trafficking protein, ARF6, as a potential therapeutic target for GNAQ/GNA11 mutated uveal melanoma. Intracellular trafficking of oncogenes is essential for cancer cells and it is our goal to discover ways to cripple tumor cells by blocking this process.