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Melanoma is one of the most lethal forms of cancer and is notoriously resistant to chemotherapy once it metastasizes, or spreads to other parts of the body. Uveal melanoma (UM) is the most common primary cancer of the eye and the second most common form of melanoma. UM has an overall mortality rate of about 50%, but once the disease spreads it is nearly always fatal. Our lab has classified our growing supply of primary uveal melanoma samples into two classes based on their gene expression, which we have named class 1 and class 2. In addition to their distinct gene expression profiles these two classes of tumors highly correlate with outcome, with the class 1 tumors almost never metastasizing and the class 2 almost always metastasizing, resulting in death. This clear distinction has led us to try to understand what is causing this aggressive phenotype in the class 2 tumors.

One key feature of the class 2 tumors is that they have lost one copy of chromosome 3, suggesting that the factor(s) responsible for the aggressive phenotype may reside here. For this reason we performed sequencing of chromosome 3 and excitingly we found one gene that is mutated (deleteriously disrupted) in almost all class 2 tumors, but rarely in the class 1 tumors. Mutations in this gene, BAP1, have also been found in cutaneous melanomas, and breast and lung cancers, suggesting that it may play a general role in tumor suppression.

Not much is currently known about BAP1's role within the cell so we hope that by manipulating BAP1 in melanoma cells in culture we can determine why disruption of BAP1 is causing melanoma to spread. By understanding the mechanism of BAP1's action, we also hope to identify novel therapeutic agents that could be used to treat metastatic melanoma.