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Developing anti-GDF6 therapeutics for treatment of advanced melanoma

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Melanoma, the leading cause of skin cancer death in the U.S., is increasing in incidence. Targeted therapies have been approved for treatment of advanced melanoma, but few patients experience extended survival benefit. In order to combat poor outcomes, new therapeutic targets are needed. Using cross-species oncogenomic analyses, our lab has identified a novel melanoma driver, Growth differentiation factor 6 (GDF6), a secreted bone morphogenetic protein (BMP) ligand that is amplified and overexpressed in human melanomas. Functional analyses show GDF6 acts via the BMP-SMAD1 pathway as a pro-survival factor in melanomas. Inhibiting GDF6 or the BMP pathway using shRNAs or the small molecule inhibitor, DMH1, induces melanoma cell death thereby abrogating melanoma growth in mouse xenografts. These results suggest GDF6 is an optimal target melanoma therapy. In order to better understand the dynamics of GDF6 signaling in melanoma cells, we are currently investigating the effect of exogenous GDF6 on cells with inhibited GDF6 expression to determine the required concentration to activate SMAD1 signaling and rescue viability. As GDF6 is a secreted ligand, we proposed developing antibodies to block the GDF6 interaction at its receptor, thereby inhibiting signaling. In collaboration with MassBiologics, we have generated a panel of monoclonal antibodies targeting GDF6. To identify antibodies capable of blocking GDF6 activity, we have devised a series of assays to eliminate antibodies from the panel. First, candidates are screened for affinity to GDF6. Second, candidates are screened for ability to block interaction between GDF6 and its receptor. Third, candidates are evaluated for ability to inhibit downstream signaling via SMAD1 pathway. After selection of final candidates, we will use a xenograft model to determine ability to inhibit melanoma growth *in vivo*. Currently, we have identified antibodies that are able to recognize GDF6 via western blot, and are proceeding to screen these antibodies for anti-GDF6 activity.

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