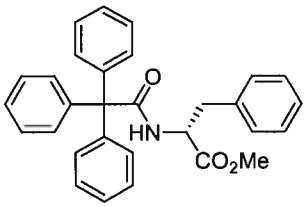
Discovery of the Biological Target of Triphenylmethylamides, Small Molecules which Potently Induce Apoptosis in Melanoma

Benjamin J. Leslie, Brittany J. Allen, and Paul J. Hergenrother

Melanoma, the least common but most serious form of skin cancer, is a growing clinical problem owing to its resistance to all known radio-, immuno-, and chemotherapeutic regimes. When confined to the epidermis, melanoma is 95% curable by surgical excision. Development of metastatic potential (associated with progression into the vertical growth phase of the tumor) renders the neoplasm inoperable, and therefore totally untreatable. Five-year survival rates for advanced malignant melanoma are less than five percent. The refractoriness of melanoma to standard cancer therapies stems from survival features intrinsic to parent melanocytes as well as mutations acquired during cancerous transformation.

Through solution-phase parallel combinatorial synthesis we have identified several small molecules containing a common triphenylmethylamide (TPMA) structural motif that exhibit potent cytotoxicity in several melanoma cell lines ($IC_{50} \cong 500$ nM). Importantly, TPMAs are up to 12 times more potent in melanoma cell lines than in bone marrow cells from healthy human donors. Several TPMAs are well-tolerated in healthy mice at high concentrations (>100 mg/kg) and efficacy trials are currently under way in mouse models of melanoma.

The efficacy of TPMAs in refractory melanoma cell types, together with mechanistic data we have compiled, suggests that TPMAs target a protein or proteins previously unexploited for chemotherapy. We have identified a small number of possible targets through affinity purification of cellular lysates from UACC-62 (melanoma) cultures followed by LC-MS/MS-based protein ID.



TPMA

IC_{50} = 620 nM UACC-62
IC_{50} = 7.00 uM Bone Marrow
MTD > 100 mg/kg Mouse
Arrests Cell in G1 Phase
Induces Apoptosis