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3070 - TARGETING FREE LIGHT CHAIN (FLC) SECRETIONAND THE UNFOLDED PROTEIN RESPONSE IN MYELOMACELLS USING VAN, A COMBINATION OF REPURPOSED DRUGS

Multiple Myeloma (MM) is a malignancy of differentiated B cells characterised by>10% neoplastic plasma cells in the bone marrow, monoclonal immunoglobulin (whole and/or free light chain; FLC) in serum/urine, lytic bone lesions and fractures, anaemia and immunodeficiency. Many patients develop renal impairment, predominantly caused by elevated serum FLCs secreted by malignant plasma cells. Despite advances in therapy, MM remains incurable and novel low toxicity therapies are urgently needed. We have identified a repurposed drug combination (VaN) of valproate (anti-epileptic)and niclosamide (anti-helminthic) with potent tumour selective additive/synergistic anti-MM activity against cell lines and primary cells at clinically achievable doses. Mechanism of action studies identified that niclosamide targets mitochondria, uncoupling oxidative phosphorylation, causing loss of mitochondrial membrane potential and inducing mitochondrial superoxide. Valproate potentiated oxidative stress through production of non-superoxide ROS. VaN treatment also rapidly inhibited FLC secretion (<2 hrs)from both MM cell lines and primary cells. VaN mediated reduction in FLC levels and anti-myeloma activity was also observed in an NSG xenograft myeloma model. Early reduction of sFLC is associated with better prognosis. Total RNA-seq and mass-spectrometry based proteomics analyses of the acetylome identified that VaN modulated several unfolded protein response (UPR) proteins. Induction of UPR was confirmed by XBP-1 alternative splicing (XBP-1s), phosphorylation of PERK and expression of CHOP. The UPR is triggered by ER stress and is already targeted clinically in MM using proteasome inhibitors (e.g. bortezomib). The addition of low-dose (1 nM) bortezomib to VaN enhanced induction of UPR and MM cell killing in vitro. In conclusion, we demonstrate that VaN and bortezomib combine to potentiate induction of ER stress and the UPR, rapidly inhibiting FLC secretion and enhancing MM cell death