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Identification of a novel compound that synergistically inhibits cell growth with BRAF inhibitor in BRAF wild type and NRAS mutant melanoma cells

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The discovery of BRAF inhibitors has revolutionized therapy for the 50% of patients with BRAFV600 mutant melanoma however BRAFWT melanomas have few effective therapies. The oncogene NRAS is activated by mutation in 15-20% of melanomas and has limited therapeutic options. Among 24 hit compounds from our recent drug screen for small molecules that enhanced the cytopathic effects of histone deacetylase inhibitors, we identified compound 012 (C-12) which unexpectedly had significant single agent activity on melanoma cell viability with limited toxicity against normal human fibroblasts. Importantly, when combined with the BRAFV600 inhibitor, vemurafenib, C-12 synergistically increased vemurafenib potency in 5 of 6 BRAFWT melanoma cell lines (Combination Index: CI<1) and dramatically reduced colony forming ability (P<0.0001). Mechanistically, combination vemurafenib+C-12 markedly increased a growth suppressor, tripartite motif (TRIM) 16 protein level and knockdown of TRIM16 in melanoma cells significantly reduced vemurafenib+C-12 induced growth inhibition suggesting that the combination exerted synergistic anti-cancer effects by inducing TRIM16 expression resulting in consequent growth arrest. Microarray analysis revealed an increase in cholesterol biosynthesis suggestive of a response to decreased intracellular cholesterol with combination treatment. Synergy studies between cholesterol inhibitors, lovastatin & U18666A and vemurafenib revealed significant synergy preferentially targeting BRAFWT melanoma in like manner to C-12. Taken together, we have identified a novel compound which works synergistically with BRAF inhibitor as an anti-cholesterol drug and specifically targets BRAFWT melanoma cells. We have further shown that statins combined with vemurafenib have significant anti-tumour activity in BRAFWT melanomas, suggesting a novel therapeutic approach.

Biography

Selina Sutton completed her PhD at the University of New South Wales in Sydney, Australia. Presently, she is a Post-doctoral researcher at the Children's Cancer Institute. She has presented her research at numerous conferences including an oral presentation at the annual Paris Melanoma Conference in 2014. She is interested in discussing research collaboration.

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