# Investigating the Anti-Melanoma Activity of Combinatorial Paclitaxel and MEK Inhibitor

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**Declaration**

I hereby declare that the candidate below is the author of this thesis, that the candidate has consulted all of the references cited, that the work of which the thesis is a record has been carried out by the candidate, except where clearly stated, and has not previously been submitted for the award of any degree.

Signed

Karamallah Al-Yousuf

I hereby declare that Karamallah Al-Yousuf has carried out his research under my supervision and has fulfilled the relevant Ordinance and Regulations of the University of Dundee, so that he is qualified to submit the following thesis in application for the degree of Doctor or Philosophy.

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## I. Abstract

Melanoma has increased considerably over the past forty years. Traditional and newly-developed anti-melanoma drugs do not produce a satisfactory therapeutic response for the treatment of late stage melanoma. Nanomedicine is a potent tool for clinicians to circumvent many of the existing shortcomings in cancer therapy. Combination of more than one drug may maximise the therapeutic response and minimise undesirable effects of the chemotherapeutic agents in cancer patients.

I developed a novel combinatorial approach that can be loaded into targeted anti-melanoma nanocarriers. Our group have been working on the development of a theranostic superparamagnetic iron oxide nanoparticle (SPION), designed to accommodate the simultaneous encapsulation of two anti-melanoma compounds, with the addition of a melanoma cell-specific targeting moiety (α-MSH) attached to the surface of the nanoparticle (NP). The selection of PTX and SEL for being loaded on α-MSH-SPION takes into consideration the anti-melanoma potency, mechanism(s) of action, physicochemical properties of each drug and their ability for embedding in the hydrophobic pocket of the NP. The synergistic ratio of PTX-SEL combination exerted limited cytotoxic effect towards normal skin cells, but was potent in melanoma cells. Also, we have analysed the drug combination *in vivo*, where the combinatorial therapy had a statistically significant effect in blocking tumour growth. In a dose- and time-dependent manner, PTX-SEL co-treatment increased oxidative stress in melanoma cells. The pro-oxidant effect of PTX-SEL is specific to melanoma rather than normal cells. These effects accompanied by mitochondrial dysfunction and increased mitochondrial ROS production indicating that mitochondria are the key source of PTX-SEL-induced-ROS production. In addition, our findings show that antioxidants antagonise the drug combination-induced melanoma cell death. Overall, our findings establish the PTX-SEL drug combination is potent and selective anti-melanoma approach with mechanistic rationale offering therapeutic benefit when loaded to α-MSH-SPIONs that can wide the horizons of clinical pharmacology field.