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Innovative Tumor-targeting Nanoformulations Containing Simvastatin and Doxorubicin Decrease Murine Melanoma Aggressiveness *In vivo* †

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Abstract: Among the most aggressive types of cancer worldwide, melanoma quickly develops resistance to traditional therapies, leading to metastasis and recurrence. With the use of a novel therapy targeting both tumor-associated macrophages and cancer cells, IL-13-PEG-LCL-SIM and PEG-EVs-DOX are being tested for whether they might diminish the aggressiveness of B16.F10 murine melanoma. Mice suffering from melanoma were intravenously given either the combination treatment or the separate SIM or DOX formulations. Western blot was used to measure the expression of different proteins, including apoptotic proteins Bcl-xL and Bax, HIF-1α, a crucial hypoxia promoter, iNOS, and NF-κB. Using HPLC, the amount of MDA, a biomarker of oxidative damage, was measured in tumor lysates. Furthermore, matrix metalloprotease (MMP-2) activity was determined as an indicator of invasion and metastasis. According to our findings, the group receiving the combination treatment significantly suppressed tumor growth (94%). Our data suggested no difference between HIF-1α protein levels in experimental conditions after various treatments compared to the control. The concentration of MDA, on the other hand, was considerably greater in the case of the combined treatment, indicating a disruption of intratumor ROS levels, which alters the balance required for HIF-1α proper activity. Slight changes were detected in the case of iNOS and NF-κB transcription factor protein expression; however, none of the nanoformulations diminished the activity of MMP-2. Nevertheless, the results showed a 1.5-fold increase in the Bax/Bcl-xL ratio, indicating that the combined sequential therapy induced a pro-apoptotic state. Our results thus imply that the evaluated active targeted combination treatment significantly suppresses the development of tumors. More research must be done to comprehend the effects of this novel active treatment on other processes that support the growth of tumors as well, such as proliferation and inflammation. Part of the study's results presented in the current abstract was published as Negrea *et al.*, 2022 (doi: 10.3389/fphar.2022.870347).

Keywords: melanoma; targeted therapy; tumor microenvironment; extracellular vesicles.

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Conflicts of Interest

The authors declare no conflict of interest.