NSC59984 nanoparticles targeting mutant p53 in advanced cancers

Raditya Nugraheni[1,2], Wafa Al-Jamal[1]

[1]School of Pharmacy, Queen's University Belfast, 97 Lisburn Road, Belfast, UK;
[2]Department of Pharmacy, University of Muhammadiyah Malang, Jalan Bendungan Sutami 188-A, Malang, Indonesia

Background: Advanced cancer encounters the emergence of drug resistance due to the high prevalence of p53 mutations. The mutation of p53 comprises 43% in all cancer type, with missense mutation being the majority. NSC59984 is a potential agent to restore p53 activity through a dual mechanism, bypassing p53 mutants to activate p73 and degrading p53 mutants. Through *in-silico* modelling, it was discovered that NSC59984 might be localized in the plasma membrane, thereby hindering the drug's ability to enter cells and reach the cytoplasm. Consequently, it is vital to encapsulate NSC59984 into nanocarriers to enhance its cell uptake and efficacy. The present work aims to develop NSC59984-loaded nanoparticles to evaluate their effectiveness in advanced and metastatic cancers.

Methods: NSC59984 was loaded into lipid-based nanoparticles and characterized using dynamic light scattering and high-performance liquid chromatography. Using resazurin assay, the half-maximal inhibitory concentration (IC50) of the free drug and nano-formulations was determined in a range of advanced and metastatic cancer cell lines with different p53 mutations. Finally, the protein expressions of p53, p73, PUMA (an apoptotic marker), and p21 (a cell cycle arrest marker) upon treatments were evaluated using western blot.

Results: NSC59984 formulations in liposomal DSPC and DOPC were successfully prepared using the thin-lipid film hydration method. The study demonstrated that the NSC59984 liposomal formulation maintained stability with consistent size, exhibiting acceptable encapsulation efficiency for *in vitro* testing. Moreover, all p53 mutant cell lines showed responsiveness to free NSC59984 treatment in both time and dose-dependent manners. Notably, NSC59984 treatment led to a significant decrease in mutant p53 levels while inducing a pronounced increase in apoptosis and cell cycle arrest markers, PUMA and p21, respectively. These marker expressions displayed time and concentration dependence, collectively indicating activation of the p53 pathway.

Conclusions: Encapsulation of NSC59984 into lipid-based nanoparticles enhances its stability and cellular uptake, thus offering a promising strategy to overcome resistance and improve treatment outcomes in advanced cancers. However, further preclinical and clinical studies are warranted to validate the efficacy and safety of NSC59984-loaded nanoparticles as a novel therapeutic intervention for advanced cancers.