Nano-encapsulated Osimertinib for Treatment of Malignant Pleural Mesothelioma (MPM)

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Purpose
Malignant pleural mesothelioma (MPM) is a rare cancer affecting the lungs' pleural cavity and is often linked to asbestos exposure. Symptoms include breathing difficulties and chest pain due to fluid buildup. Current treatments involve chemotherapy and surgery, offering limited relief. The cisplatin-pemetrexed combination improves survival by a moderate 3 months but has side effects. Seeking alternatives, we explore Osimertinib (OSI), a tyrosine kinase inhibitor for non-small cell lung cancer for the treatment of MPM. To enhance delivery, OSI was entrapped in biodegradable nanoparticles for inhalation directly to the affected lungs, addressing its low aqueous solubility.

Methods
OSI was tested against the MPM cell line MSTO-211H at various concentrations. Cells were seeded in a 96-well plate and treated with OSI ranging from 0.7 to 100 µM, with cytotoxicity measured using a Cell Titer Blue assay after 48 hours to determine the IC50 value via GraphPad Prism. To counter OSI's limited solubility, it was encapsulated in PLGA nanoparticles using an emulsification-sonication method with different concentrations of PVA stabilizer and varied sonication time. Nanoparticle drug content was analyzed using UPLC, and their size and surface charge were measured. Finally, the cytotoxicity of the prepared nanoparticles was evaluated similarly to OSI.

Results
Results showed OSI's effectiveness against MSTO cells with an IC50 of 6±1.1 µM, indicating potential for MPM treatment. OSI was successfully encapsulated in PLGA nanoparticles using emulsification-sonication. Optimal encapsulation (43±4.8%) and 4.5 % drug loading were achieved with 1% PVA and 4 minutes of sonication. The optimized nanoparticles had a size of 198.5 ± 9.8 nm and a polydispersity index (PDI) of 0.1, indicating a uniform size distribution. Their zeta potential was reported to be -17.6 ± 1.2 mV. The cytotoxicity of PLGA-OSI nanoparticles was comparable to OSI alone, with an IC50 of 7.8 ± 2.1 µM.

Conclusion
OSI holds promise for MPM treatment, exhibiting potent toxicity in MPM-diseased cells. Further research can explore its mechanism of action and impact on molecular pathways. Entrapping OSI in PLGA nanoparticles addresses solubility limitations. Optimized PLGA-OSI warrants investigation into aerosolization, cellular uptake, and cytotoxicity in spheroid cultures.

Keywords: Repurposing, Mesothelioma, PLGA nanoparticles