# Biodegradable Polymeric Multilayer Capsules for Therapy of Lung Cancer

**Tuesday, 30 Jun 2020**


**Authors**

Marina V Novoselova [1,2‡], Hui Mun Loh [3‡], Daria B Trushina [1,4,5], Avanee Ketkar [6], Tatiana O Abakumova [2], Timofei S Zatsepin [2], Mitali Kakran [1], Agata Maria Brzozowska [1], Hooi Hong Lau [1], Dmitry A Gorin [2], Maria N Antipina [1*], Anna I Brichkina [3, 6*]

[1] Institute of Materials Research and Engineering, A*STAR , 2 Fusionopolis Way , Innovis, #08-03, Singapore , 138634 , Singapore.

[2] Skolkovo Institute of Science and Technology , Bolshoy Boulevard 30, bld. 1 , Moscow 121205 , Russia.

[3] Institute of Molecular and Cell Biology, A*STAR , 61 Biopolis Drive , Proteos, Singapore 138673 , Singapore.

[4] I.M. Sechenov First Moscow State Medical University , Bol'shaya Pirogovskaya Ulitsa 19c1 Moscow 119146 , Russia.

[5] A.V. Shubnikov Institute of Crystallography of Federal Scientific Research Centre "Crystallography and Photonics" of Russian Academy of Sciences , Leninskiy Prospekt, 59 , Moscow 119333 , Russia.

[6] Institute of Molecular Oncology , Philipps University of Marburg , Member of the German Center for Lung Research (DZL), Hans-Meerwein-Str. 3 35043 Marburg , Germany.

‡These authors contributed equally

*Correspondence: anna.brichkina@staff.uni-marburg.de

antipinam@imre.a-star.edu.sg

Published in ***ACS Applied Material & Interfaces*** 2020, 12, 5, 5610–5623

Publication Date: January 16, 2020

Download: https://pubs.acs.org/doi/10.1021/acsami.9b21381

## ABSTRACT

Formulated forms of cancer therapeutics enhance the efficacy of treatment by more precise targeting, increased bioavailability of drugs, and an aptitude of some delivery systems to overcome multiple drug resistance of tumors. Drug carriers acquire importance for anti-cancer interventions via targeting tumor-associated macrophages with active molecules capable to either eliminate them or change their polarity. Although several packaged drug forms have reached the market, there is still a high demand for novel carrier systems to hurdle limitations of existing drugs on active molecules, toxicity, bioeffect, and stability. Here, we report a facile assembly and delivery methodology for biodegradable polymeric multilayer capsules (PMC) with the purpose of further use in injectable drug formulations for lung cancer therapy via direct erosion of tumors and suppression of the tumor-promoting function of macrophages in the tumor microenvironment. We demonstrate delivery of low-molecular-weight drug molecules to lung cancer cells and macrophages and provide details on in vivo distribution, cellular uptake, and disintegration of the developed PMC. Poly-Larginine and dextran sulfate alternately adsorb on a ~500 nm CaCO3 sacrificial template followed by removal of the inorganic core to obtain hollow capsules for consequent loading with drug molecules, gemcitabine or clodronate. The capsules further compacted upon loading down to ~250 nm in diameter via heat treatment. A comparative study of the capsule internalization rate in vitro and in vivo reveals the benefits

of a diminished carrier size. We show that macrophages and epithelial cells of the lungs and liver internalize capsules with efficacy higher than 75%. Using an in vivo mouse model of lung cancer, we also confirm that tumor lungs better retain smaller capsules than the healthy lung tissue. The pronounced cytotoxic effect of the encapsulated gemcitabine on lung cancer cells and the ability of the encapsulated clodronate to block the tumor-promoting function of macrophages prove the efficacy of the developed capsule loading method in vitro. Our study taken as a whole demonstrates the great potential of the developed PMC for in vivo treatment of cancer via transporting active molecules, including those that are water-soluble with low molecular weight, to both cancer cells and macrophages through the bloodstream.

**FIGURE**

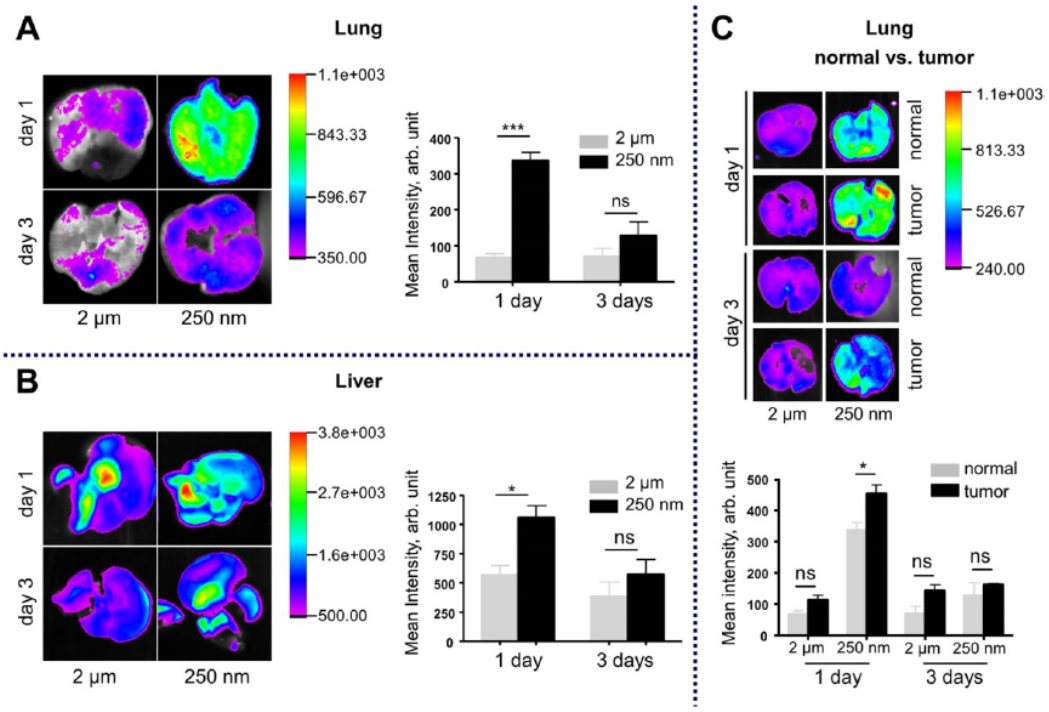


**FIGURE LEGEND**

Delivery of large (~2 µm) and compacted (~250 nm) PMC to the mouse lungs and liver. Bioluminograph ex vivo images of lungs and liver of mice sacrificed 1 or 3 days after intravenous injection of TRITC-labeled capsules and respective tissue diagrams depicting the fluorescence intensity of the label plotted as the mean and standard deviation. The data plots were derived from the arbitrary unit color scales shown next to the respective sets of images. (A) Lungs and (B) liver of healthy C57/B6 mice. (C) Lungs of healthy C57/B6 mice and K-rasG12D mice bearing lung cancer.