**MULTIVALENT RUBBER-LIKE RNA NANOPARTICLES FOR TARGETED CO-DELIVERY OF PACLITAXEL AND MIRNA TO SILENCE THE DRUG EFFLUX TRANSPORTER AND LIVER CANCER DRUG RESISTANCE**

*Hongzhi Wang a,b,1,* ***Satheesh Ellipilli*** *a,b,1, Wen-Jui Lee d, Xin Li a,b, Mario Vieweger a,b,Yuan-Soon Ho d, Peixuan Guo a,b,c \**

*1Co-first authors (authors contributed equally)*

*aCenter for RNA Nanobiotechnology and Nanomedicine, The Ohio State University, Columbus, OH, USA bDivision of Pharmaceutics and Pharmacology, College of Pharmacy, The Ohio State University, Columbus, OH, USA. cDorothy M. Davis Heart and Lung Research Institute, The Ohio State University, Columbus, OH, USA. dSchool of Medical Laboratory Science and Biotechnology, College of Medical Sciences and Technology, TMU Research Center of Cancer Translational Medicine, Graduate Institute of Medical Sciences, College of Medicine, Taipei Medical University, Taiwan.*

**ABSTRACT:**Hepatocellular carcinoma (HCC) is one form of liver cancer and the third leading cause of cancer-related death worldwide. The liver functions as a filter analog to border customs detoxify the chemicals and metabolites from the blood. Moreover, liver cancer cells overexpress drug exporters leading to chemoresistance and reduced chemotherapeutic effect on liver cancer. RNA nanoparticles demonstrated to have rubber-like properties that lead to efficient therapeutics delivery to the tumor site and fast renal clearance after systemic injection. Therefore, a new multivalent RNA nanoparticle is designed harboring three copies of hepatocyte targeting-ligands, one copy of miR122, and 24 copies of Paclitaxel to overcome the drug effluxion and chemoresistance. The hepatocyte targeting ligands and the rubber-like RNA nanoparticles allowed for enhanced targeting ability to the HCC tumors thus, bind and internalize into the liver cancer cells. The RNA nanoparticles delivered the miR122 and PTX to the liver cancer cells due to their rubber-like property and the receptor-mediated endocytosis. The miR122 silenced the drug exporters as well as oncogenic proteins thus, sensitize the liver cancer cells for PTX resulted in more cancer cell death. The miR122 and PTX synergistically reduced the cancer cell growth that is further confirmed by HSA (Highest Single Agent) synergy model. The RNA nanoparticle predominantly accumulated in HCC tumor sites and efficiently inhibited the tumor growth after systemic injection to mice xenografts bearing liver cancer. This study demonstrates the potential use of the rubber-like multivalent RNA nanoparticles to conquest liver cancer.