Telmisartan Produces Better Intratumoral Nanoparticles Distribution and Anticancer Effects Compared to Losartan
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Purpose
To study the effect of Telmisartan (AT1 blocker and PPAR-gamma partial agonist) and Losartan (AT1 blocker) on nanoparticles intratumoral distribution and anticancer effects in lung cancer

Methods
Paclitaxel nanostructured lipid carriers (P-NLCs) were prepared and administered intravenously. Fluorescent polystyrene nanoparticles (200 nm) beads were used to study the intratumoral distribution pattern of nanoparticles after Telmisartan and Losartan treatments. Orthotopic and Metastatic Non small cell lung cancer (NSCLC) models in nu/nu mice were used. Animals were grouped as 1) Control, 2) Telmisartan, 3) Losartan, 4) Telmisartan+P-NLCs 5) Losartan+P-NLCs 6) P-NLCs groups. 1 week after the cancer cells injection, Telmisartan (1.12 mg/kg) and Losartan (4.5 mg/kg) were administered by inhalation delivery at alternative days. 2 weeks after the inhalation delivery, P-NLCs (5 mg/kg, every third day total 3 doses) were administered by i.v. route. 4 weeks after the inhalation delivery. Animals were sacrificed and tumor weight and volumes were measured. Tumor fibrous nature was characterized by estimating collagen-1, TGF β-1 and Masson's trichrome staining. Further, cleaved caspase-3, AT1 receptors, MMP-9 expressions were studied by immunohistochemistry and western blotting.

Results
Inhalation delivery of Telmisartan and Losartan produced significant antitumor effects in both tumor models. Lung tumor weights and tumor volumes were significantly decreased in inhalation groups. Comparatively, Telmisartan at 1/4th dose produced better anticancer effects than Losartan. Better survival was observed with Telmisartan and Losartan compared to untreated controls. Further, P-NLCs s produced better tumor regression in inhalation groups compared to single drug treatment groups and control groups. Significant increase in the collagen-1 content and TGF-beta indicate the high fibrous nature of lung tumors. Telmisartan and Losartan treatment resulted in the decrease in tumor fibrosis. Due to high fibrous nature nanoparticles distribution into the tumor was found to be insufficient, whereas, treatment with Telmisartan and Losartan resulted in the better nanoparticles distribution. Due to decreased tumor fibrosis in Telmisartan and Losartan treated groups, Paclitaxel nanoparticles (P-NLCs) distribution was better, which in turn exhibited synergistic anticancer effects.

Conclusion
Telmisartan by virtue of its dual pharmacophoric nature could be an ideal candidate for combination therapy to improve the nanoparticles intratumoral distribution and anticancer effects.