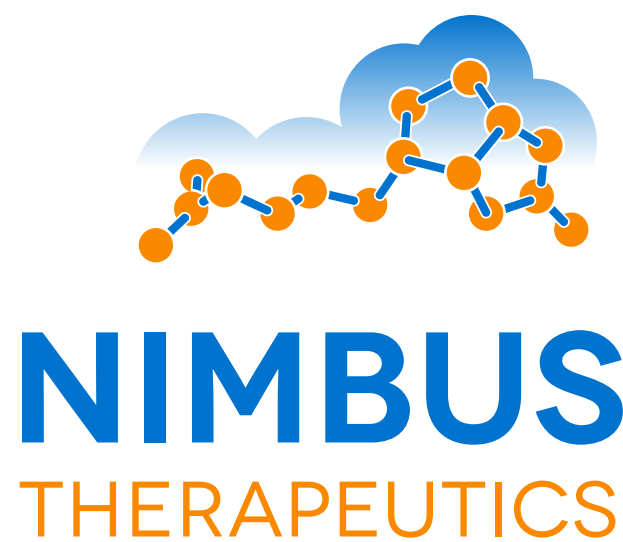


Combination Therapy with a Liver Selective Acetyl CoA Carboxylase Inhibitor ND-654 and Sorafenib Improves Efficacy in the Treatment of Cirrhotic Rats with Hepatocellular Carcinoma

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Abstract
#3781

OVERVIEW

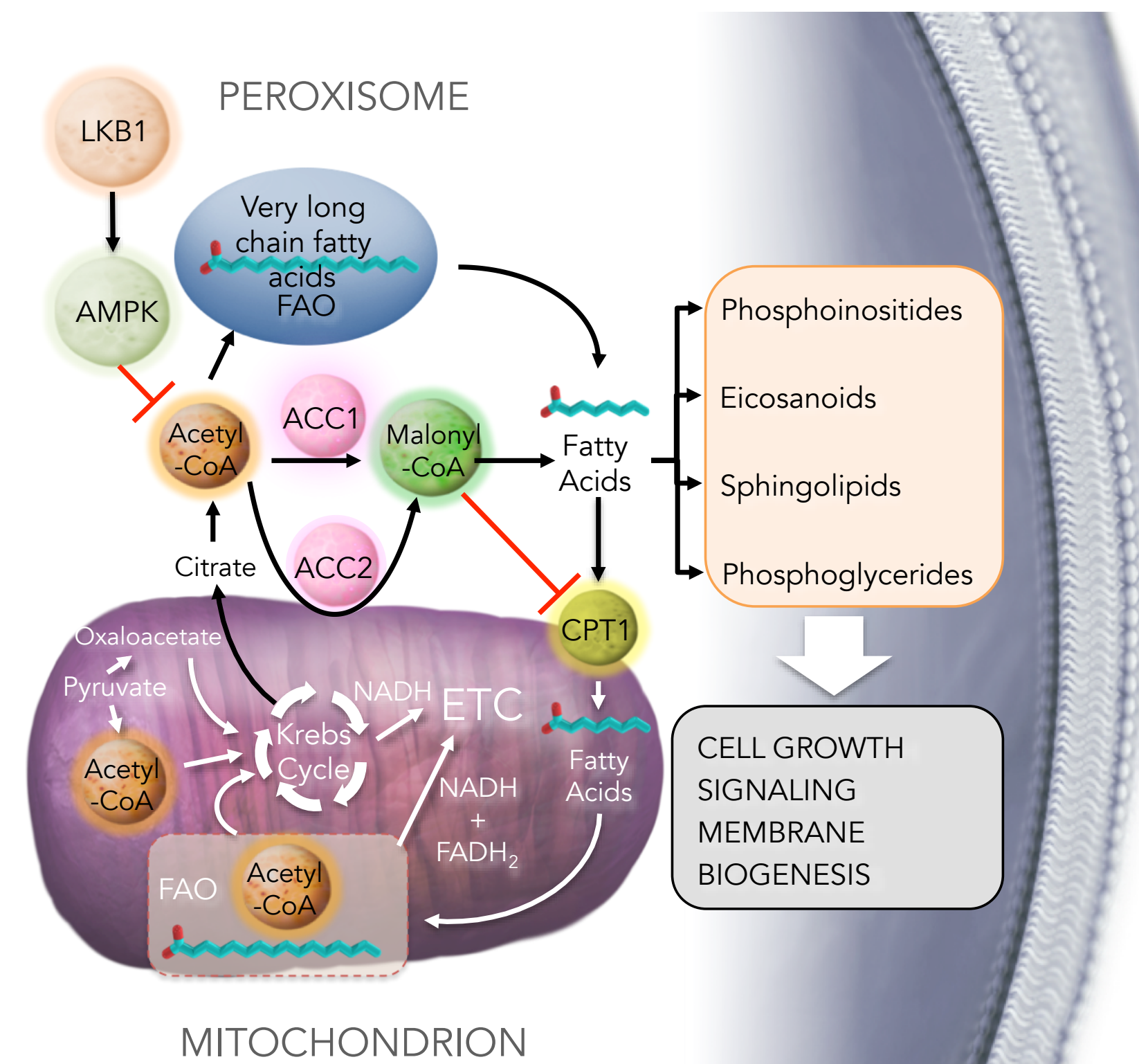
ACC: An Emerging Tumor Metabolism Target

- Current treatment options for HCC are limited, and as such, prognosis is extremely poor with a 5-year survival less than 12%

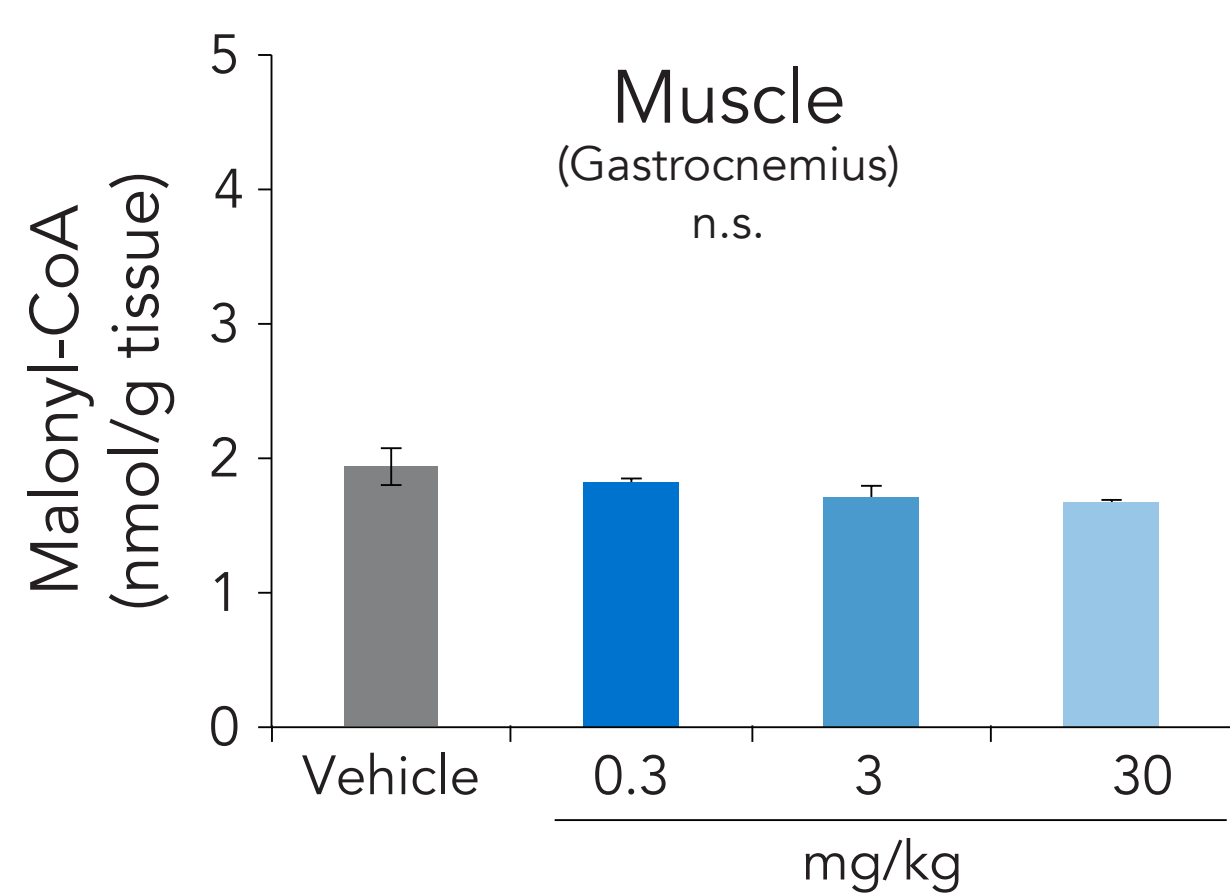
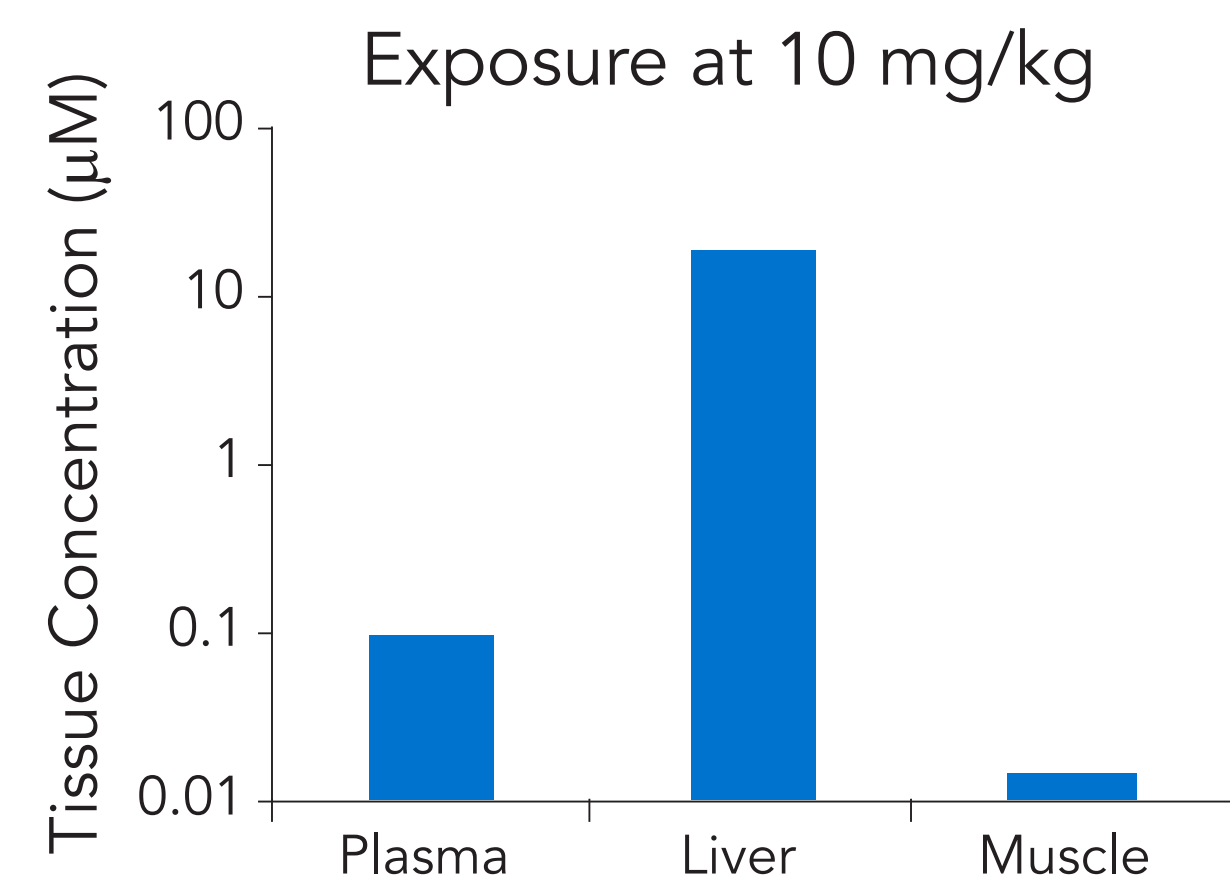
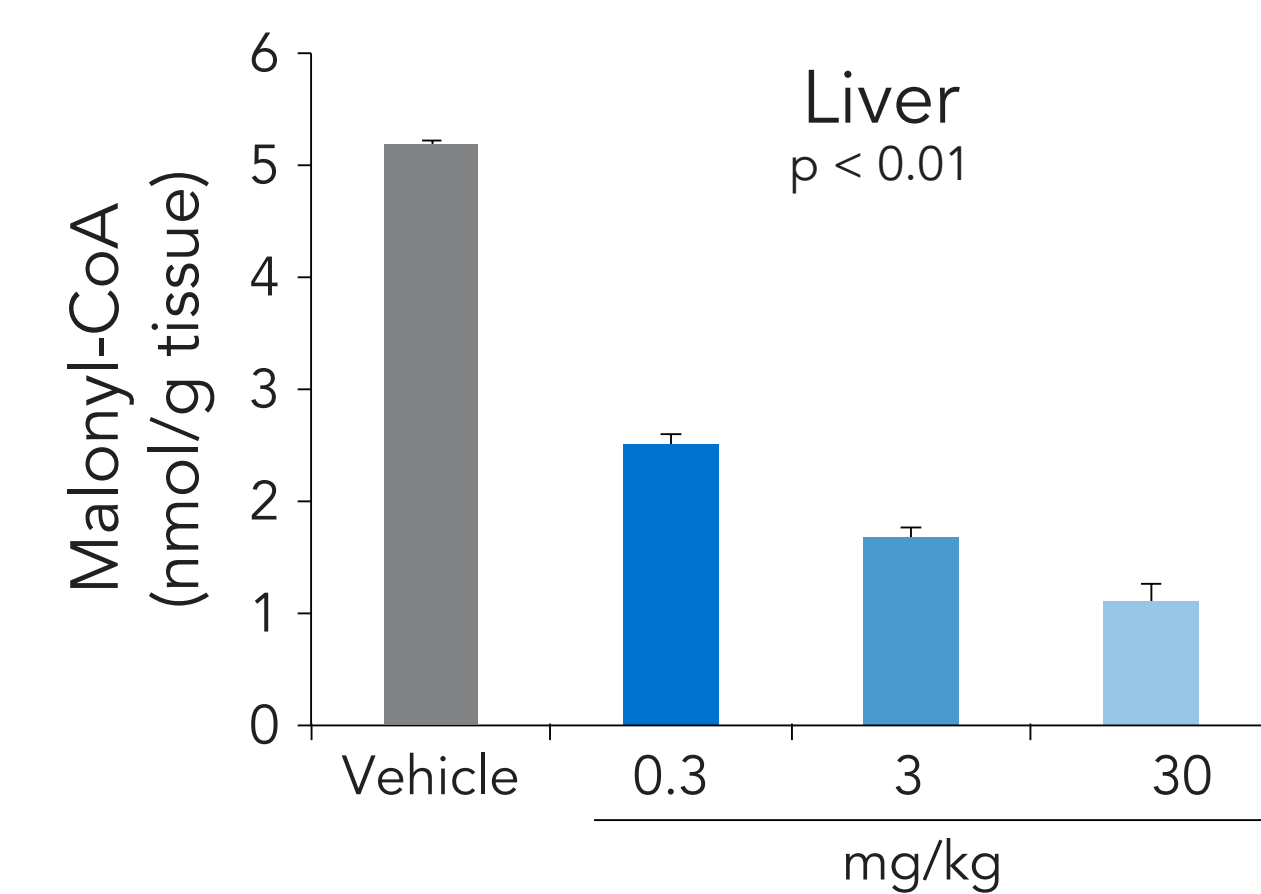
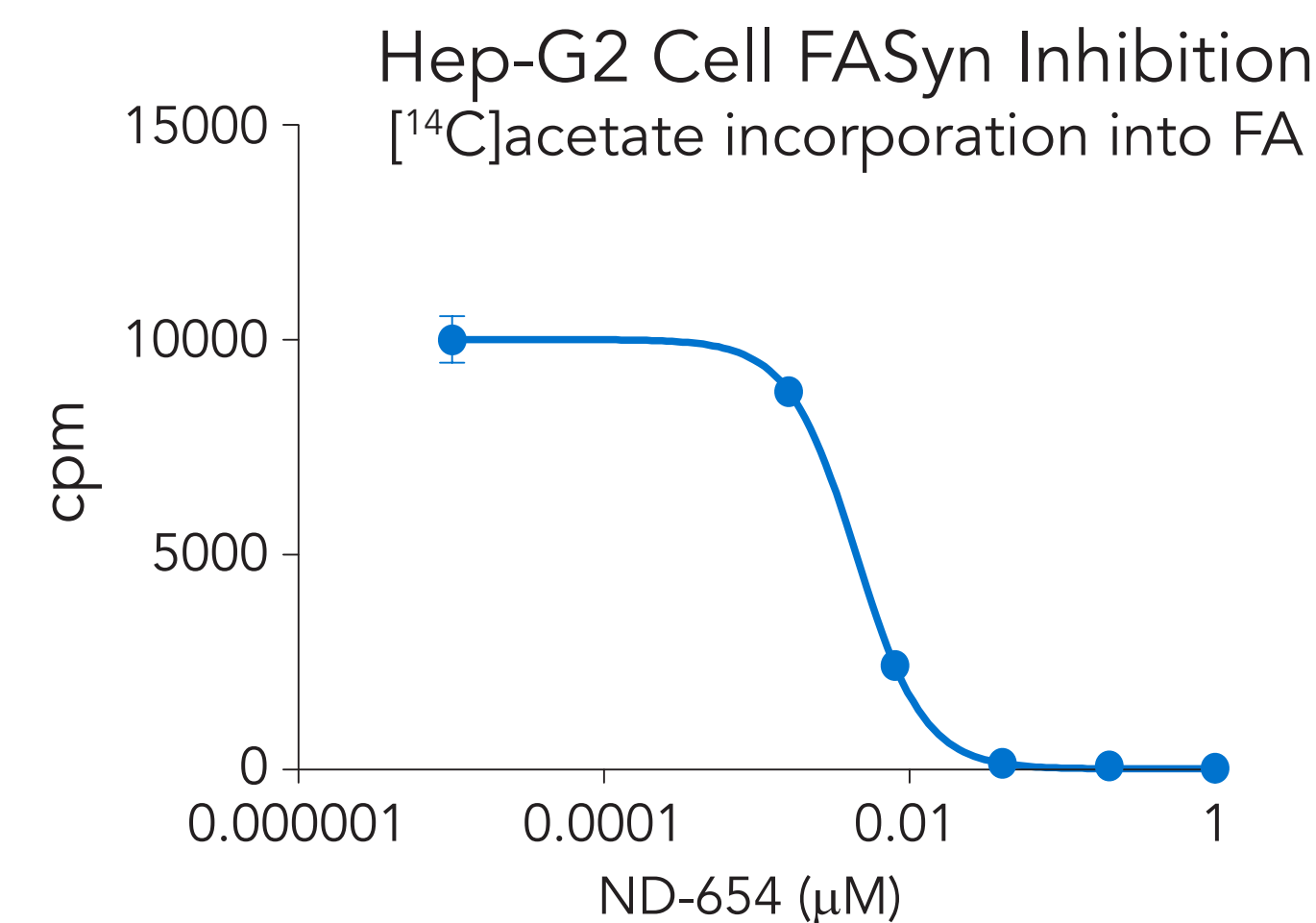
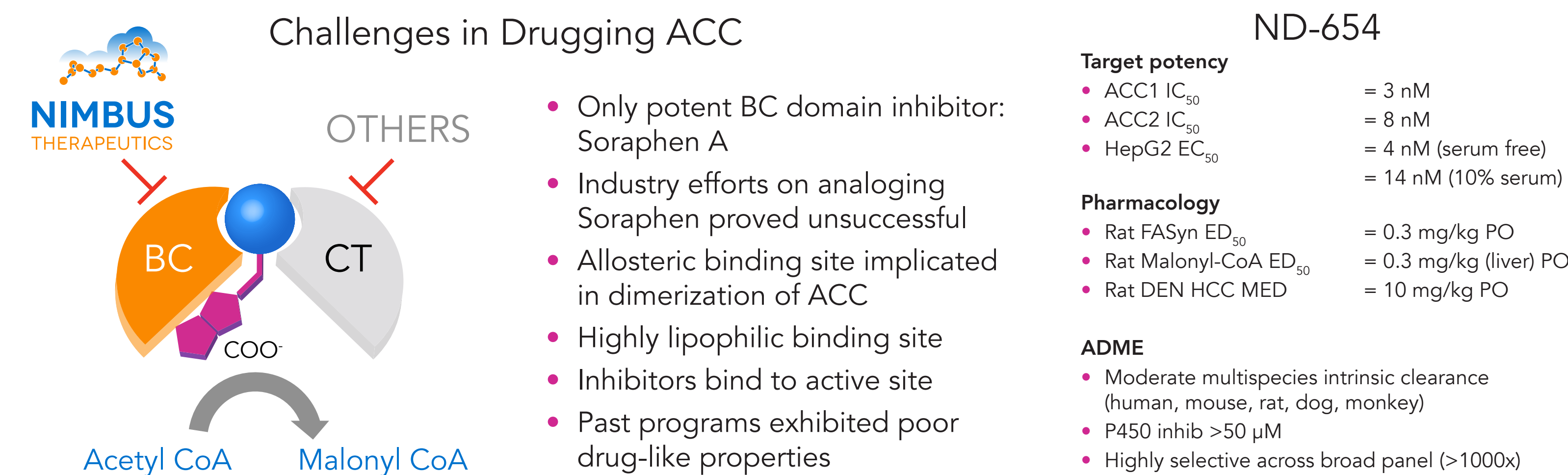
- Metabolic attenuation is a promising approach to cancer therapy, and rate-limiting steps in key biosynthetic pathways are particularly attractive targets. **Hepatospecific** ND-654 is a potent allosteric inhibitor of the lipid master regulator Acetyl CoA Carboxylase (ACC)

- ND-654 demonstrates excellent PK/PD relationships in the target tissue, the liver (exposure vs Malonyl CoA reduction), and is effective at modifying cirrhotic and HCC relevant endpoints in the DEN model

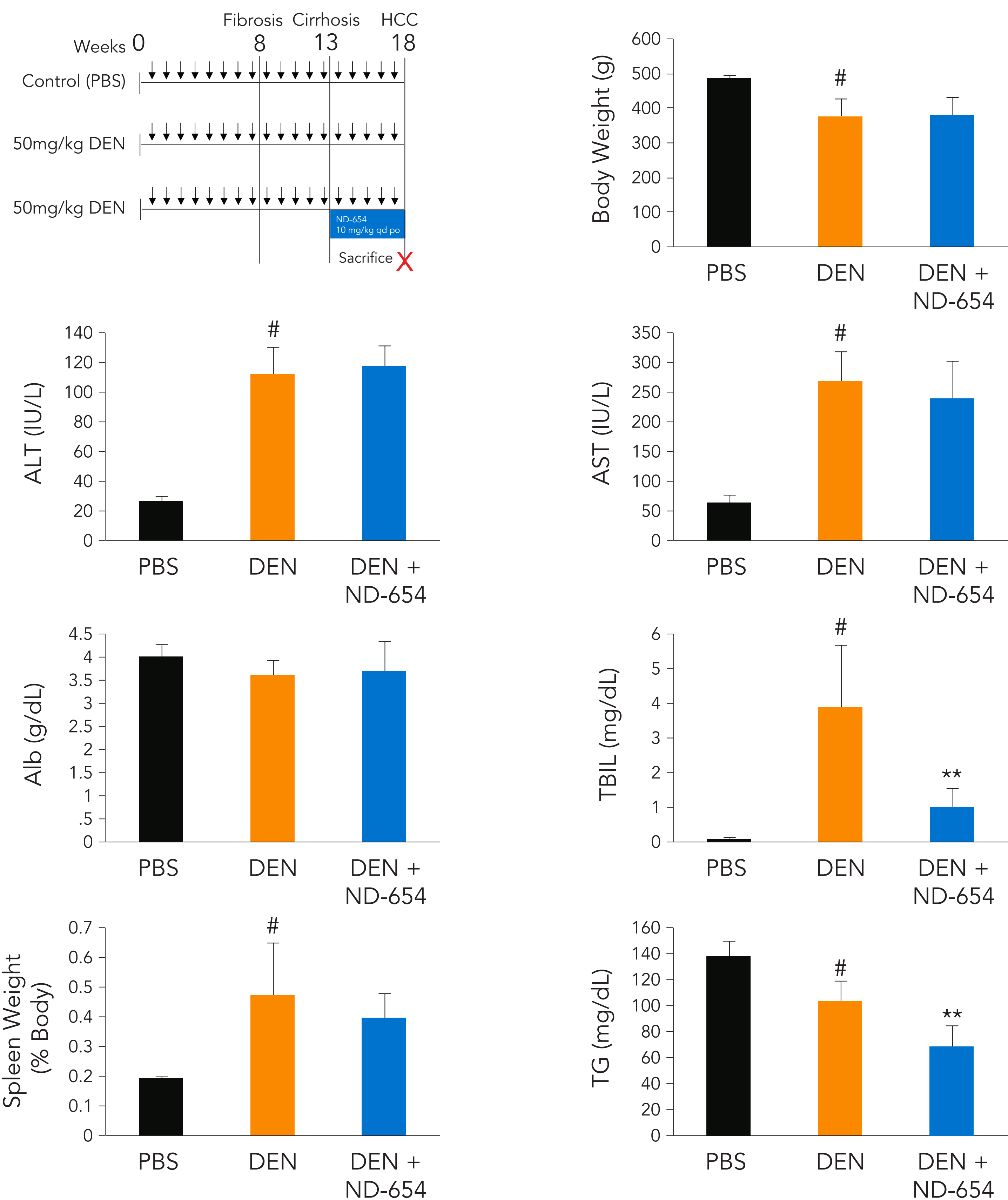
- ND-654 demonstrates the ability for tissue targeted ACC inhibition to decrease tumor burden, liver fibrosis and prolong survival in the highly aggressive rat DEN model of HCC



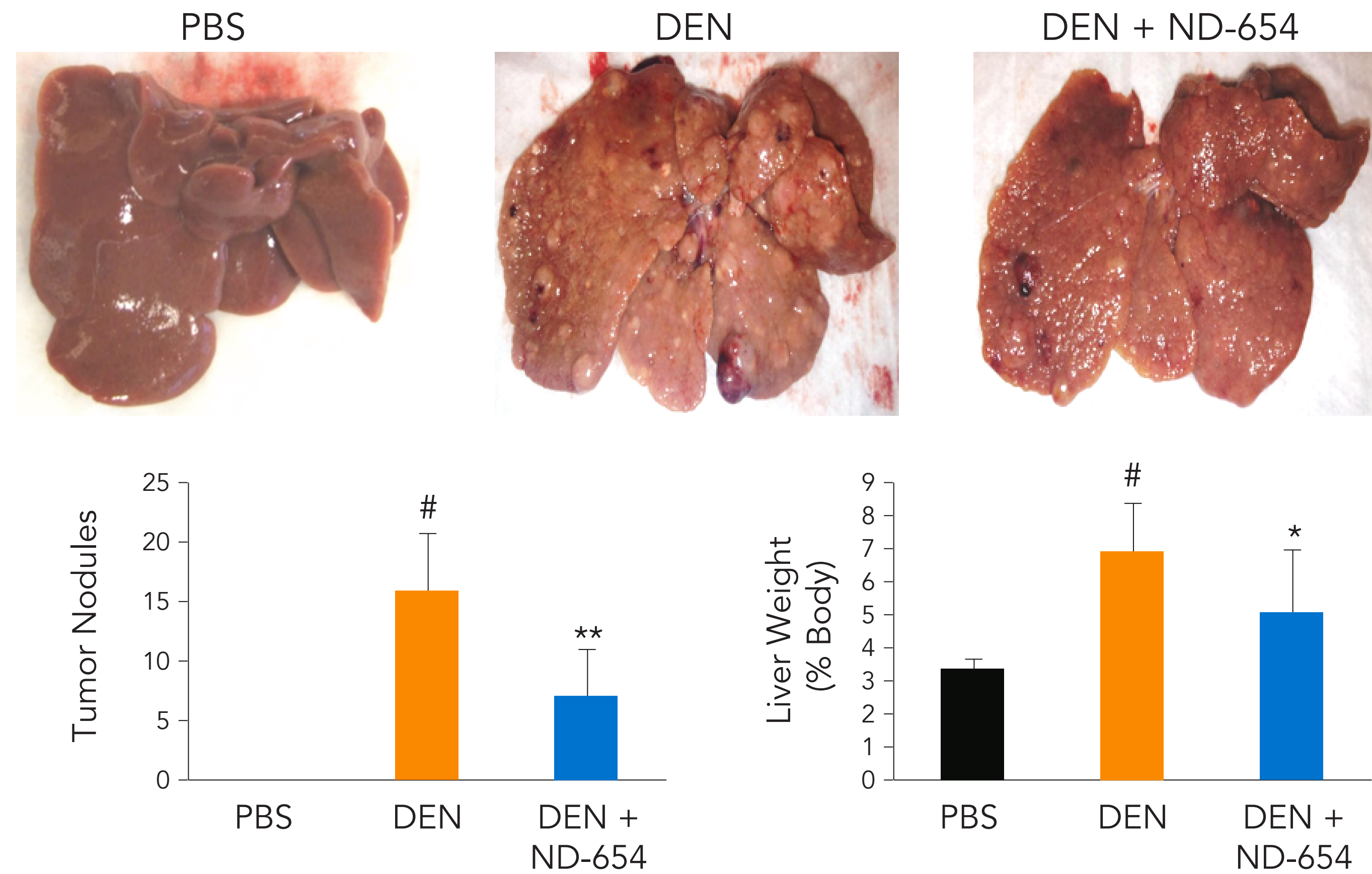
1. ND-654 Targets Allosteric Site in Biotin Carboxylase Domain



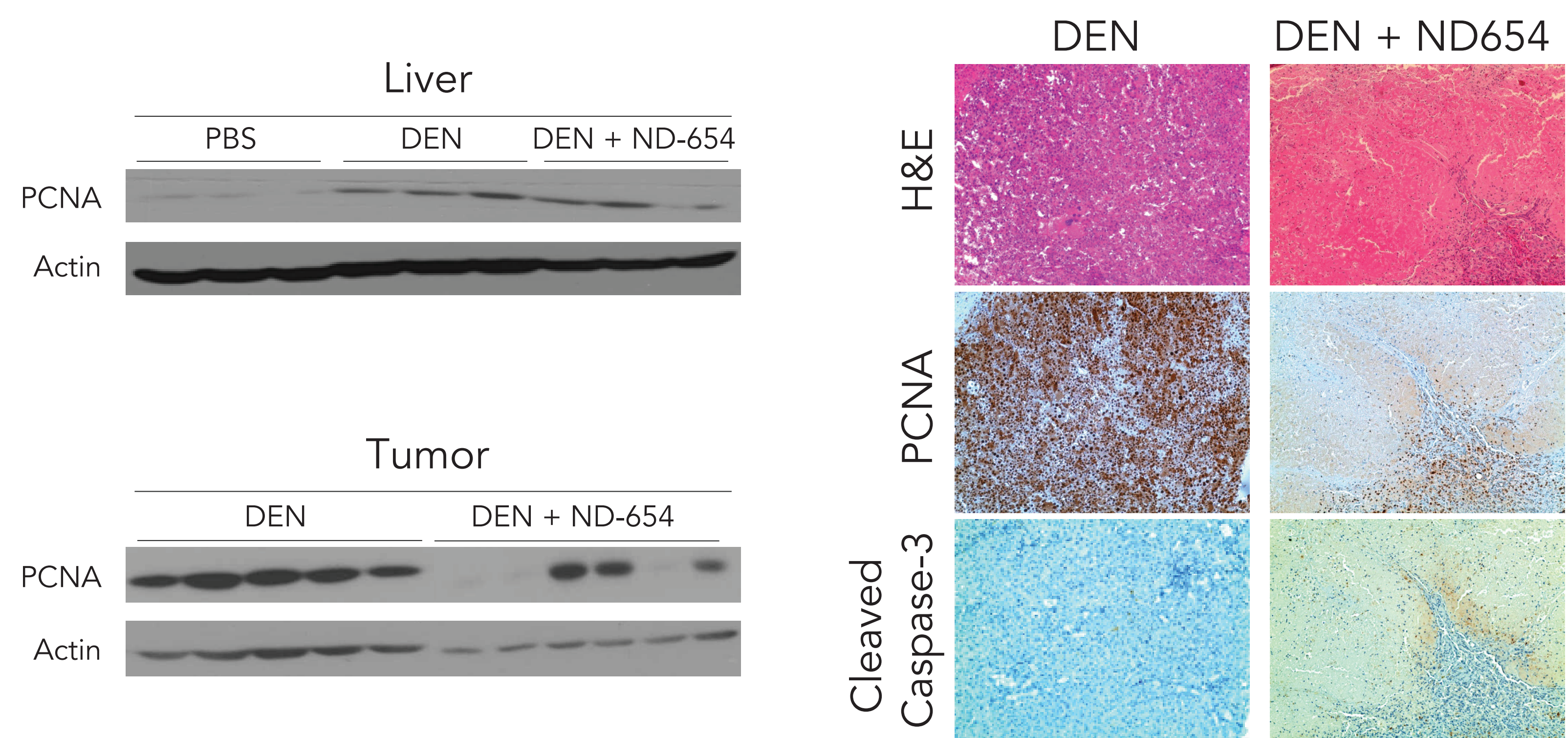
2. ND-654 is Well-Tolerated in the DEN Rat Model



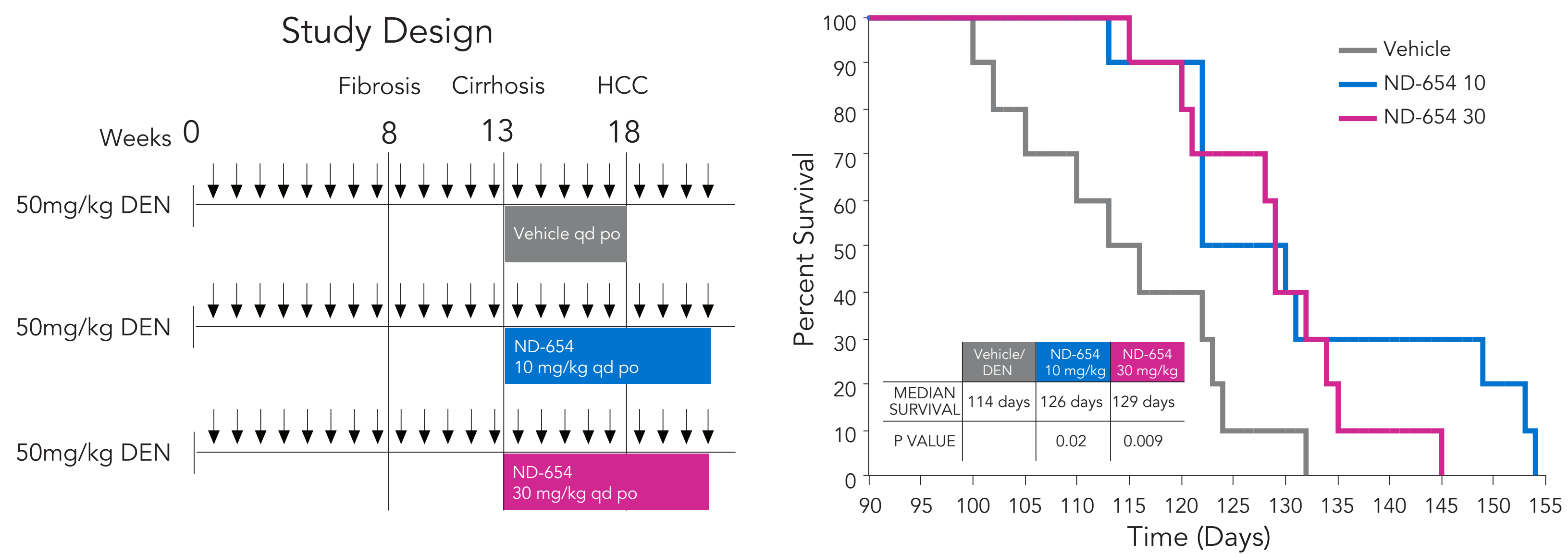
3. ND-654 Results in Marked Reduction of Tumor Nodules



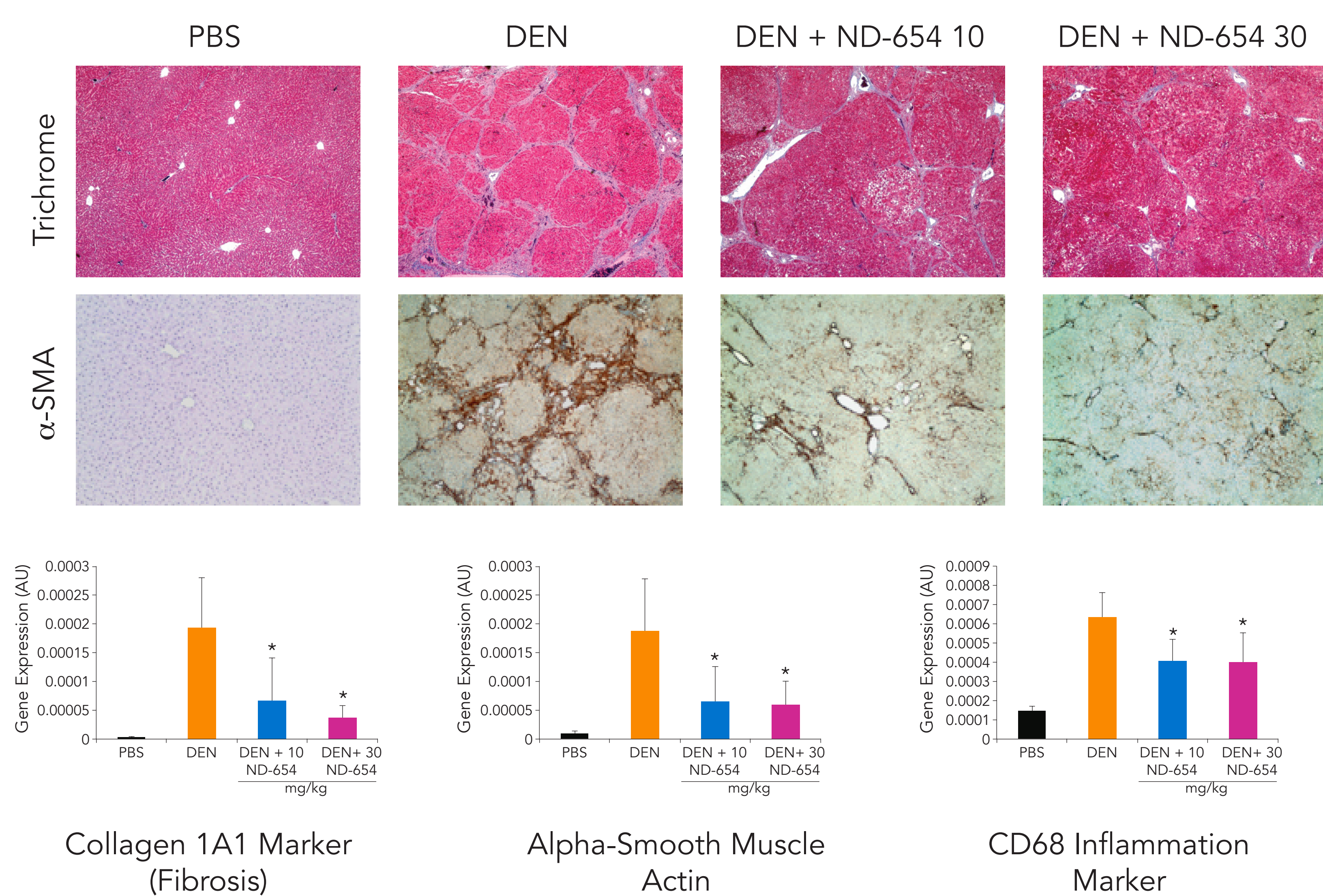
4. ND-654 Decreases Tumor Proliferation and Increases Tumor Necrosis



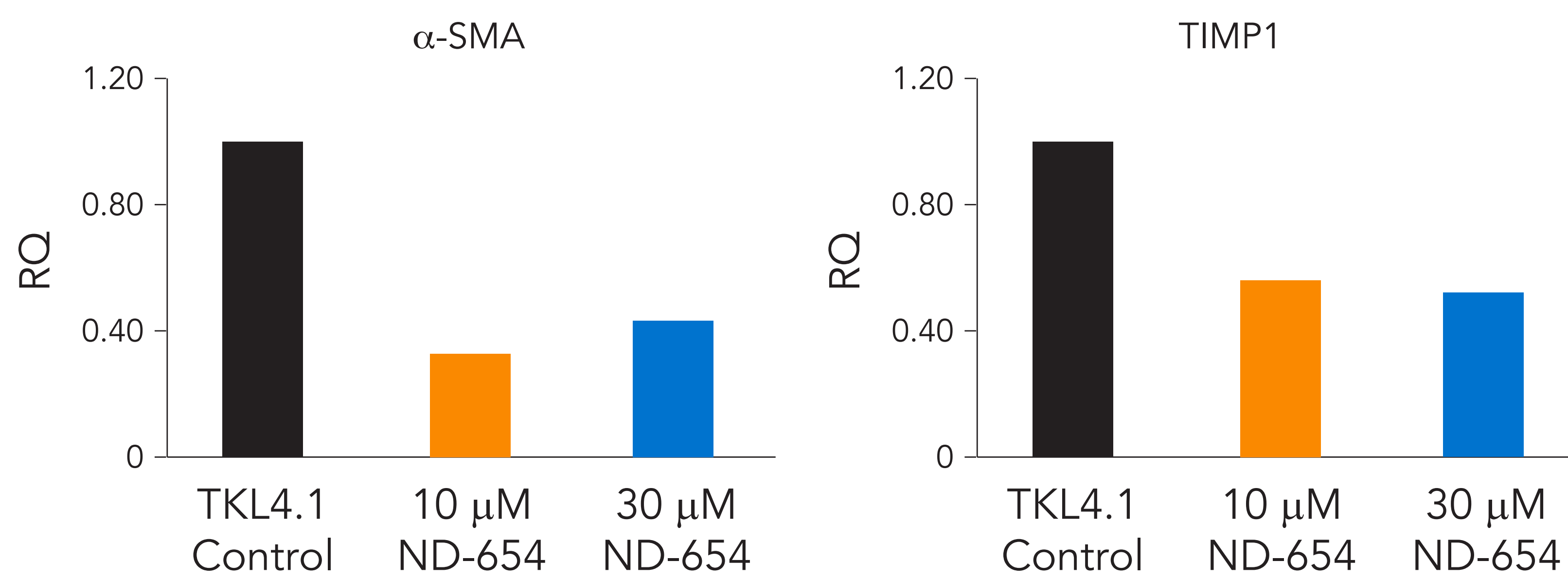
5. ND-654 Significantly Improves Survival in the Aggressive DEN Model



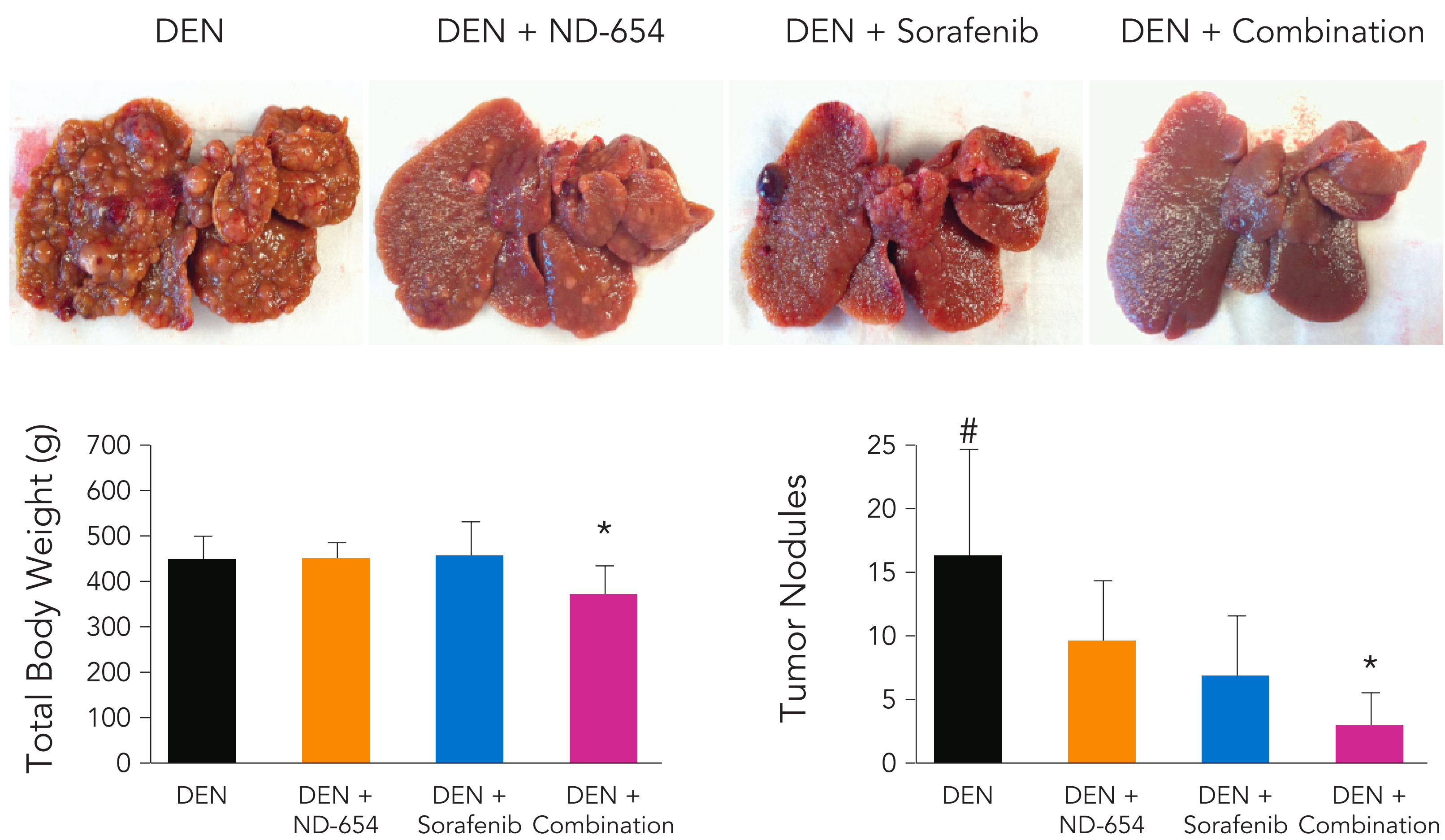
6. ND-654 Decreases Markers of Fibrosis and Inflammation



7. ND-654 Decreases Markers of Fibrosis and Inflammation in Primary Human Stellate Cells *in vitro*



8. ND-654 Improves the Efficacy of Sorafenib



CONCLUSION

- ND-654 preferentially biodistributes to the liver where it inhibits ACC activity without generating liver toxicity
- ND-654 inhibits HCC development by decreasing tumor proliferation and causing tumor necrosis
- ND-654 reduces markers of fibrosis and inflammation in the liver of DEN rat *in vivo* efficacy model and in primary human stellate cells *in vitro*
- ND-654 improves overall survival and the efficacy of sorafenib in the DEN rat model
- Our results therefore provide further evidence that *de novo* fatty acid synthesis is an important mediator of hepatic carcinogenesis
- Selective inhibition of hepatic ACC is a potential therapeutic strategy for hepatocellular carcinoma