Bioactive lipids have been shown to play both pro- and anti-clotting regulatory roles in platelet function resulting in modulation of hemostasis and thrombosis. While much is known about COX-1 regulation and the role of its free fatty acid metabolites in regulation of the platelet, less is known about how 12-LOX and its fatty acid eicosanoids mediate these essential functions. Nearly 33% of deaths annually are associated with cardiovascular disease and platelet activation is essential to arteriothrombotic clots leading to myocardial infarction and stroke. Therefore a greater understanding of the role of 12-LOX in this process is needed and may represent a novel target for prevention of thrombosis. Our group has developed a highly selective 12-LOX inhibitor to target 12-LOX in the platelet and determine its potential role in platelet activation and thrombotic risk. Here, we show for the first time the in vivo utility of inhibiting 12-LOX. In human platelets run through a microfluidics system at arterial shear, treatment with the 12-LOX inhibitor ML355 was shown to be more effective at decreasing platelet adhesion to collagen compared to aspirin. In vivo, platelet accumulation at the site of injury in a number of thrombotic models in the mouse was prevented in the presence of ML355. Importantly, bleeding, a common side effect of platelet inhibition, was not affected, supporting 12-LOX as an important enzyme in regulation of hemostasis and thrombosis in vivo (Adili et al. Arterioscler Thromb Vasc Biol 2017). These observations, coupled to the earlier observation by our group that inhibition or ablation of 12-LOX was effective in preventing immune-mediated thrombosis in human platelets and mouse models (Yeung et al. Blood 2014), raised the question of whether inhibition of 12-LOX might be a viable treatment of immune-mediated thrombocytopenia and thrombosis (ITTs). To address this question, transgenic mice expressing human immune receptor FcγRIIa but not ALOX12, were retro-orbitally injected with a fluorescent antibody for the platelet receptor GPIIX to induce ITT-like symptoms. Blood was collected at several time points to assess platelet count and the mice were sacrificed after 4 hours to determine the degree of thrombosis in vascular beds such as the lungs. While induction of ITT resulted in over 80% platelet loss within an hour and significant thrombosis in the lungs within 4 hours, animals lacking 12-LOX showed protection from both of these pathologies. Hence, targeting 12-LOX with ML355 demonstrates that 12-LOX is a viable antiplatelet target for arteriothrombotic events while exhibiting limited bleeding.