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Comment on 'Pharmacological inhibition of protein tyrosine phosphatase 1B protects against atherosclerotic plaque formation in the LDLR$^{-/-}$ mouse model of atherosclerosis'

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We read with great interest the recent article by Thompson and colleagues [1] which reported the effects of inhibiting protein tyrosine phosphatase 1B (PTP1B) on the development of atherosclerosis within low-density lipoprotein receptor deficient (LDLR$^{-/-}$) mice receiving either chow or high-fat diet. In this study, the authors conducted two experiments in which mice received single or five doses of the specific PTP1B inhibitor, trodusquemine. In both experiments, the investigators reported that when compared with controls, mice receiving trodusquemine exhibited a significant decrease in weight gain paralleled by marked improvements in glycaemic control and lipid profile. A key finding was the observation of a significantly lower atherosclerotic plaque area within the aortic root in high fat fed mice which received trodusequemine, compared with the saline controls. This led the authors to conclude that inhibition of PTP1B '*. . . resulted in both the reduction and reversal of atherosclerotic plaque formation under obesogenic conditions*.' Identification of drugs with the ability to reverse the severity of established atherosclerosis has a significant potential to improve patient care. The findings of this study are therefore of great interest to the field and have led to substantial media attention.

We believe, however, that the authors' statements are misleading, as 'reversal' implies a documented regression in the size of atherosclerotic plaques over time. In order to assess this experimentally, it would be necessary to conduct a longitudinal study in which at least two assessments of the atherosclerotic burden of each mouse were conducted (e.g. pre- and post-treatment). In contrast, data presented by Thompson and colleagues [1] suggest that atherosclerotic burden was assessed in a cross-sectional manner in samples harvested from culled mice at the end of the experiment. This design does not permit the measurement of atherosclerotic severity prior to administering intervention and relies on an assumption that the degree of atherosclerosis is similar between groups. The severity of diet-induced atherosclerosis varies between mice and we believe that it is impossible to conclusively state that plaque area decreased in response to PTP1B therapy, without first quantifying the extent of disease within each animal. Recent studies have measured the progression of atherosclerosis in experimental animals through the use of non-invasive imaging modalities such as ultrasound, computed tomography and MRI (reviewed in [2,3]), and we believe that such approaches are needed to definitively demonstrate whether trodusqemine is capable of reversing established atherosclerosis.

We congratulate Thompson and colleagues on their interesting work which has great translational potentail, but urge caution in the interpretation of the presented data

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Competing interests

The authors declare that there are no competing interests associated with the manuscript.

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Abbreviation

PTP1B, protein tyrosine phosphatase 1B.

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