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Letter to the Editor

Author's Response to: Rebuttal to: Simvastatin Treatment Does Not Ameliorate Muscle Pathophysiology in a Mouse Model for Duchenne Muscular Dystrophy, Verhaart et al. 2020

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We would like to point out that the batch of chow used in the Aartsma-Rus group contained the same dose of simvastatin and was prepared in an identical manner by the same supplier (Research Diets) as the chow used by Whitehead et al, using the instructions Dr. Froehner provided us with. The chow used by the Wells group was ordered from a different supplier but had an identical dose [2].

The key question is why in our hands this identical dose delivered in the same manner, resulted in much lower plasma levels. An obvious experiment would be to use a simvastatin chow batch used by Whitehead et al in our mice, to see whether this would result in higher plasma concentrations. This was an experiment we were willing to perform. Despite repeated requests from us, Dr. Froehner did not provide us with the chow he used.

Whitehead et al cite a number of papers that confirm that simvastatin delivered via chow can result in therapeutic effects [1]. However, the majority of cited studies did not examine plasma levels of simvastatin and metabolites. The one that did, reported lower levels than Whitehead et al. (3), despite administering a much higher dose of simvastatin in the chow [6].

Whitehead et al cite [1] two recent papers that confirm the therapeutic effects of simvastatin treatment in the *mdx* mouse model [4, 5]. However, the first citation does not mention a dose [4], while the second used delivery via oral gavage of 20 mg/kg simvastatin [5], which would amount to a higher dose of simvastatin than the one we or Whitehead et al used. While these studies confirm the therapeutic effect of simvastatin treatment in *mdx* mice, they do not confirm that this can be achieved at doses that are in the range of what humans use.

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