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Response to 'Comment on 'The potential contribution of tumour-related factors to the development of FOLFOX-induced sinusoidal obstruction syndrome''

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Sir,

We read with interest the observations of Lentschener *et al.*, who have attempted unsuccessfully to replicate our murine model of FOLFOX-induced sinusoidal obstruction syndrome (SOS) (Robinson *et al*, 2013a, b). While the drug treatment regimen and experimental conditions used in these experiments were broadly similar to those used by us, we do note some key important differences.

During our initial attempts to develop a model of FOLFOX-induced SOS, we similarly found that animals maintained on standard chow diets did not develop the histological features of SOS – a finding described in our original description of this model (Robinson *et al*, 2013a). We observed that switching to a purified diet (D01060501, Research Diets Inc, New Brunswick, NJ, USA) but maintaining an otherwise identical experimental protocol did lead to the development of histological features of SOS. We have previously hypothesised (although not proven) that this may be attributable to the presence of phytoestrogens in standard animal diets, which have a protective effect on the development of liver injury (Ascencio *et al*, 2004; McCarty *et al*, 2009). While the diet utilised by Lentschener *et al.* does contain reduced phytoestrogens as compared with standard chow diets (Global Rodent diet-2016, Harlan Laboratories, Madison, NJ, USA), these are still present. Of course it may be that other constituents in the diet are having a role, but we have not explored this.

It would be also interesting to know which substrain of C57BL/6 mouse was utilised by Lentschener *et al.* In our experiments, we utilised the C57BL/6J substrain that differs from the C57BL/6N substrain by the deletion of exons 7–11 of the nicotinamide nucleotide transhydrogenase (*Nnt*) gene that has key roles in the mitochondrial response to oxidative stress (Mekada *et al*, 2009; Simon *et al*, 2013). As we have previously reported, oxidative stress appears to have a key role in the development of SOS, and therefore the choice of C57BL/6 substrain may be particularly important in this context, although we haven't specifically explored this.

The final observation to make is that all drugs in our description of the model were obtained from Sigma-Aldrich (Dorset, UK), whereas those used by Lentschener *et al,* were from different sources. Whether these different preparations have the same pharmacological characteristics *in vivo* is not known.

While we do believe that FOLFOX-induced SOS can be modelled in mice, we acknowledge that the work of Lentschener *et al,* does highlight how subtle differences in the experimental protocol can have a significant impact on the reproducibility of this model.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

Ascencio C, Torres N, Isoard-Acosta F, Gomez-Perez FJ, Hernandez-Pando R, Tovar AR. (2004) Soy protein affects serum insulin and hepatic SREBP-1 mRNA and reduces fatty liver in rats. *J Nutr* **134**(3): 522–529.

McCarty MF, Barroso-Aranda J, Contreras F. (2009) Genistein and phycocyanobilin may prevent hepatic fibrosis by suppressing proliferation and activation of hepatic stellate cells. *Med Hypotheses* **72**(3): 330–332.

Mekada K, Abe K, Murakami A, Nakamura S, Nakata H, Moriwaki K, Obata Y, Yoshiki A. (2009) Genetic differences among C57BL/6 substrains. *Exp Anim* **58**(2): 141–149.

Robinson SM, Mann J, Vasilaki A, Mathers J, Burt AD, Oakley F, White SA, Mann DA. (2013a) Pathogenesis of FOLFOX induced sinusoidal obstruction syndrome in a murine chemotherapy model. *J Hepatol* **59**(2): 318–326.

Robinson SM, Mann DA, Manas DM, Oakley F, Mann J, White SA. (2013b) The potential contribution of tumour-related factors to the development of FOLFOX-induced sinusoidal obstruction syndrome. *Br J Cancer* **109**: 2396–2403.

Simon MM, Greenaway S, White JK, Fuchs H, Gailus-Durner V, Wells S, Sorg T, Wong K, Bedu E, Cartwright EJ, Dacquin R, Djebali S, Estabel J, Graw J, Ingham NJ, Jackson IJ, Lengeling A, Mandillo S, Marvel J, Meziane H, Preitner F, Puk O, Roux M, Adams DJ, Atkins S, Ayadi A, Becker L, Blake A, Brooker D, Cater H, Champy MF, Combe R, Danecek P, di Fenza A, Gates H, Gerdin AK, Golini E, Hancock JM, Hans W, Hölter SM, Hough T, Jurdic P, Keane TM, Morgan H, Müller W, Neff F, Nicholson G, Pasche B, Roberson LA, Rozman J, Sanderson M, Santos L, Selloum M, Shannon C, Southwell A, Tocchini-Valentini GP, Vancollie VE, Westerberg H, Wurst W, Zi M, Yalcin B, Ramirez-Solis R, Steel KP, Mallon AM, de Angelis MH, Herault Y, Brown SD (2013) A comparative phenotypic and genomic analysis of C57BL/6J and C57BL/6N mouse strains. *Genome Biol* **14**(7): R82

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