LETTER

# Targeting the microbiota–gut–brain axis to modulate behavior: Which bacterial strain will translate best to humans?

We have read with great interest the paper by Bravo et al. (1), which showed that *Lactobacillus rhamnosus* (*Lr* JB-1) can modulate behavior and CNS biochemistry in healthy mice via the vagus nerve. This is a very well conducted study on an emerging topic in neurogastroenterology: the role of the microbiota–gut–brain axis in modulation of behavior and mood. We have previously shown that the probiotic *Bifidobacterium longum* (*Bl* NCC3001) normalizes behavior and CNS biochemistry (2–4) in mice with mild colitis, an effect also mediated via the vagus nerve (3, 4). Interestingly, both bacteria modulate enteric neuron excitability (3–5), suggesting that enteric to vagus nerve signaling is an important means of communication along the microbiota–gut–brain axis.

We want to highlight some differences and discrepancies in the behavior-modulating capacity of these bacteria. We have shown that *Bl* NCC3001 produces an anxiolytic effect in two different models of anxiety-like behavior as assessed by light/dark preference and step-down tests (2–4). In contrast, the effect of *Lr* JB-1 varies considerably depending on the experimental paradigm used: an anxiolytic-like effect observed in open field and elevated plus maze tests vs. an anxiogenic effect reported in the fear-conditioning model (increased emotional learning is an anxiety-like behavior) with no significant effect observed against stress-induced hyperthermia (SIH) (1). A possible explanation for this discrepancy is that Bravo et al. used normal animals whereas our studies used models of anxiety-like behavior induced by infection or mild colitis (2–4). Indeed, we have shown that another strain of *L. rhamnosus* NCC4007 (LGG) produces no improvement in anxiety-like behavior in such mouse models (2). The lack of effect on SIH in the Bravo study is consistent with this conclusion as SIH employs an acute sensitization stimulus and as such these animals are not, strictly speaking, normal.

Although NCC4007 and JB-1 strains of *L. rhamnosus* are similar, they are not genetically identical (1) and it remains to be determined whether the JB-1 strain possesses a different efficacy profile than NCC4007 in animal models of anxiety. Demonstration of efficacy with the JB-1 strain in such models is of pivotal importance to better understand the role of this strain in modulation of behavior and likely translation to humans.

The differences between our previous study and that of Bravo et al. may be clinically relevant when attempting to translate these results into human trials in patients with gastrointestinal disorders and psychiatric comorbidity. It is difficult to predict how results in animal models will translate to humans; however, the predictive value of behavioral models is often best when the efficacy is consistently anxiolytic and relevant disease models are used. Around one-third of irritable bowel syndrome (IBS) patients report a postinfective history and IBS is associated with low-grade gut inflammation. For this reason, in addition to studies in normal animals, models involving an anxiogenic stimulus with relevance to the pathogenesis of the IBS (2–4) are desirable when preclinically evaluating the possible therapeutic effects of probiotics.

***Peter G. McLean, Gabriella E. Bergonzelli, Stephen M. Collins, and Premysl Bercik***[1]
*McMaster University, Hamilton, ON L8N 3Z5, Canada*

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Author contributions: P.G.M., G.E.B., S.M.C., and P.B. wrote the paper.

Conflict of interest statement: P.G.M. and G.E.B. are employees of Nestle Switzerland, and S.C. and P.B. have received research grants from Nestle Switzerland.

[1]To whom correspondence should be addressed. E-mail: bercikp@mcmaster.ca.


www.pnas.org/cgi/doi/10.1073/pnas.1118626109