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BRIEF COMMUNICATION ARISING

Geng et al. reply

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REPLYING TO Y. Rao *Cell Res.* 30, https://doi.org/10.1038/s41422-020-0344-3 (2020).

The accompanying comment by Dr. Rao, suggests that there is an omission of citation of 12 previous publications in our Wang et al. paper.[1] We disagree with the suggestion for the following reasons.

We believe that the 12 publications cited by Dr. Rao do not have sufficient relevance to the Wang et al. paper.[1] The past decades have witnessed an explosive growth in our understanding of the pathogenesis of Alzheimer's disease (AD), which is a very complicated process. The Wang et al. paper specifically reports a distinct and novel mechanism of GV-971 in the treatment of AD, from the angle of gut microbiota and associated neuroinflammation. Out of the 12 publications Dr. Rao mentioned, four are review articles[2–5] that summarized the therapeutic potential and mechanistic insights of saccharides in treating AD in general,[2,3] the transport of neuroactive drugs across blood-brain barrier,[4] or strategies for designing small molecules to inhibit β-amyloid aggregation;[5] none of these reviews specifically discussed GV-971. One research article reported the chemical synthesis of a series of new and truncated derivatives of GV-971, which did not focus on GV-971 per se.[6] One publication is a non-peer-reviewed meeting abstract summarizing the unpublished results of GV-971 at the time.[7] Another paper investigated the potential effect of GV-971 on Parkinson's disease, which is different from AD.[8] The rest five papers[9–13] are only remotely related to the Wang et al. paper: three papers investigated the impacts of GV-971 on β-amyloid aggregation and neuronal toxicity,[9] β-amyloid-induced astrocyte activation,[10] or scopolamine-induced memory impairment,[11] one attempted to identify GV-971 binding proteins in neurons in vitro,[12] and the other one preliminarily examined gene expression alterations caused by GV-971 in a β-amyloid dependent mouse model.[13] Therefore, we think these 12 publications are not suitable to be cited, as their relevance to the Wang et al. paper is rather minimal.

As a matter of fact, we have committed decade-long efforts to better understand the molecular mechanisms and therapeutic utility of GV-971. Thus far, we have discovered multifaceted mechanisms which collectively contribute to the therapeutic effectiveness of GV-971 in AD patients. The effect of GV-971 on gut microbiota and associated neuroinflammation is perhaps one of the most important aspects. We have also accumulated large amount of data that support the impact of GV-971 on β-amyloid aggregation and associated neuronal damage and cognitive decline both in vitro and in vivo. We aim to wrap up those studies and publish our findings soon.

Dr. Rao raised a personal concern of GV-971's multifaceted mechanisms reported by us, and he claimed that he had "never come across a single drug with so many targets for curing or alleviating one disease". We disagree with this comment. In fact, it is NOT uncommon that marketed drugs target multiple pathways for its intended therapeutic effects. Taking metformin, the most widely used oral type 2 diabetic medication, as an example, it executes glycemic control through distinct mechanisms in multiple tissues, including decreasing hepatic glucose production, reducing intestinal glucose absorption, and improving glucose uptake and utilization by peripheral tissues etc.[14] While it has long been thought to act as an inhibitor of mitochondrial complex 1 and activator of AMPK,[14] recently increasing evidence suggests that the altered gut microbiome also contributes to the therapeutic effects of metformin in treating type 2 diabetes.[15–17]

ADDITIONAL INFORMATION

Competing interests: XYW, GQS, TF, JZ, XKC, JY, SSC, YXG, LFR, GQZ, SYY, WL, CD, DBY and CRG are full-time employees of Shanghai Green Valley Pharmaceutical Co., Ltd. The other authors declare no competing interests.

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