

## Authors responses to review comments:

### Specific Comments to Authors:

- (1) These were largely due to the complex intracellular signalling by Melanocortin 4 receptor, and the understanding by the Melanocortin 4 receptor receptor, its expression and downstream signalling enabled the identification of agonists which mimic its physiological actions. This article is very innovative and provides good ideas for the potential pathogenesis and intervention measures of obesity, which is worth learning for researchers. The article has a clear train of thought, abundant research literature included, and can closely analyze and discuss the relationship between MC4R and obesity--The hypothalamic leptin-melanocortin pathway is central to the regulation of appetite and weight, where leptin activates proopiomelanocortin (POMC) neurons, leading to the production of melanocortin peptides; these in turn act on melanocortin 4 Receptor to suppress appetite and increase energy expenditure. Melanocortin 4 receptor mutations are responsible for syndromic and non-syndromic obesity. as well as potential mechanisms of action. It has good logic and clear hierarchy, Setmelanotide, a Melanocortin 4 receptor agonist has been approved for use in the treatment of obesity due to Melanocortin 4 receptor mutations. It did not have adverse effects on heart and blood pressure in humans while having a substantial weight loss effect, with a favourable therapeutic index. Setmelanotide, a Melanocortin 4 receptor agonist has been approved for use in the treatment of obesity due to Melanocortin 4 receptor mutations. It did not have adverse effects on heart and blood pressure in humans while having a substantial weight loss effect, with a favourable therapeutic index. The same time ,In addition to MC4R agonists and antagonists, inverse agonists are potential areas for investigation; these include AgRP and its mimics for Melanocortin 4 receptor.
- (2) **Authors response:** The **authors thank the reviewer** for highlighting the essence of the manuscript and commenting about its applicability for further work
- (3) **Company Editor-in-Chief:**
- (4) I have reviewed the Peer-Review Report, full text of the manuscript, all of which have met the basic publishing requirements of the World Journal of Experimental Medicine and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Before final acceptance, the **author(s) must add a table/figure** (medical imaging) to the manuscript.
- (5) **Authors response:** We have **added a Figure (Fig 1) and two tables (Table 1,2)** to the manuscript as advised by the Company Editor-in-Chief