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September 18, 2025.

Subject: Letter in support of the proposal **DISC0-17488** entitled **'A novel platform to rescue neurodevelopmental disorders caused by haploinsufficiency'**.

Dear Members of the Application Review Subcommittee,

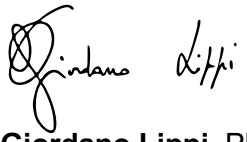
We are grateful to the Grant Working Group for reviewing a large number of applications covering many broad topics. The Review Summary for our application was overwhelmingly positive, identifying many strengths, such as the high significance, the '*potential for strong impact*', and a feasible and innovative approach supported by mapping technologies that are '*far superior to modelling*' and for which the investigators are '*world experts*'. We are very excited at the prospect of conducting this critical research that will identify new therapies for diseases of haploinsufficiency.

This letter is to briefly discuss the only criticism in the Review Summary: the perceived lack of specificity of antisense oligonucleotides (ASOs) targeting repressive regulatory elements. Namely, one Reviewer stated: '*one concern is that the proposal does not address the fact that regulatory elements are, to this reviewer's knowledge, not generally gene-specific. Thus, identification and blockade of negative regulatory elements on haploinsufficiency neurodevelopmental disorder (NDD) genes would likely have extensive effects on expression of many other genes, potentially limiting the potential usage of this approach.*' While the Reviewer is correct in stating that the sequence of the repressive regulatory elements is not gene-specific, it is critical to notice these elements are much shorter than ASOs. For example, the binding site for a microRNA (a repressor of protein production) is only 5-7 nucleotides, while ASOs are typically 20-30 nucleotides. Thus, **we can use the regions flanking the negative regulatory elements to design ASOs that are highly specific to one negative regulatory element on one NDD gene and have no significant complementarity to other genes**. We have demonstrated such high specificity in previous publications (Lippi et al. **Neuron** 2017, Dulcis et al. **Neuron** 2018, Taylor et al. **Elife** 2023), and many colleagues have seen similar results, thus **ASOs' high specificity is now common knowledge**. For this reason, ASOs are considered an exciting new tool for precision medicine approaches, and they are increasingly used in the clinic, as demonstrated by 11 ASO-based FDA-approved therapies. Importantly, co-investigator Dr. Kim-McManus holds an FDA-approved investigational new drug (IND) application for

an individualized ASO tailored to a patient with developmental epileptic encephalopathy due to a causal *SCN2A* variant.

We hope this brief explanation can resolve the only criticism raised during review. We thank you for your support of this application.

Sincerely,



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