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Magn. Reson. Discuss., referee comment RC1
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Comment on mr-2021-20

Mingjie Zhang (Referee)

Referee comment on "Small-molecule inhibitors of the PDZ domain of Dishevelled proteins interrupt Wnt signalling" by Nestor Kamdem et al., Magn. Reson. Discuss., https://doi.org/10.5194/mr-2021-20-RC1, 2021

In this manuscript, Kamdem et al. first used virtual screening to identify lead compounds that may have potential to bind to the PDZ domain of Dishevelled (Dvl) scaffold protein. They then used NMR chemical shift perturbation-based screening together with X-ray structure guided optimizations to derive reasonably high affinity Dvl PDZ binding compounds. These compounds display certain selectivity in binding to Dvl PDZ. Importantly, the designed compounds (e.g. Compound 18) has low toxicity and good activity in inhibiting Wnt signaling in cell-based assays. Thus, the compounds identified in the current study may hold potential for therapeutic applications targeting the Wnt pathway.

Overall, the experiments performed in this study are comprehensive and of high quality. Results presented in the manuscript are convincing. The paper is well-written. This reviewer supports the publication of this manuscript in this special issue of MR after minor revision.

Minor concerns:

- There appear discrepancies in the bindings of compound 3289-8625 to Dvl PDZ in the literature (Grandy et al, 2009) and in the current study based on the data in Fig. S7. The assay condition used in the current study may not allow the authors to derive

accurate binding constant of the interaction. The authors need to address this issue.

- In line 185&187: “R2” should be “R1”.