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Response to Comment on: "Mmrn1 expression defines a novel subset of hematopoietic stem cells and leukemia stem cells with great self-renewal potential"

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Response to Comment on: "Mmrn1 expression defines a novel subset of hematopoietic stem cells and leukemia stem cells with great self-renewal potential"

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Running title:

Response to Deciphering the role of Mmrn1 in HSCs

Authors' contributions:

All authors contributed to the conception, writing, and revision of this response and approved the submitted version.

We thank Dr. Shen for the thoughtful comments regarding our recent article published in Haematologica.[1-2] The two points raised are timely and clinically relevant: that exploring the interactions between Mmrn1-high leukemic stem cells (LSCs) and bone marrow (BM) niche, and refining the molecular subtyping of acute myeloid leukemia (AML).

Shen hypothesized that Mmrn1 may mediate the physical interactions between LSCs and BM niche via integrins or stromal cell surface receptors. This speculation is well-supported: Multimerin-1 uniquely possesses both an RGD integrin-binding motif and EGF-like repeats among the EMILIN family, and Emilin-2, another family member, has been shown to regulate BM hematopoietic progenitor pools as an extracellular matrix component.[3-4] Furthermore, Peng et al. recently demonstrated that MMRN1 activates EGFR/STAT1/NPL signaling in LSCs, driving sialylglycan-mediated immune evasion via the Siglec axis, while concurrently maintaining self-renewal through EGFR/STAT5/CD9.[5] Although our study showed no difference in homing between $Mmrn1^{-/low}$ and $Mmrn1^{high}$ HSCs, this does not preclude a niche-anchoring role in the leukemic context where the BM microenvironment is actively remodeled.[6]

We also agree that classifying AML into “M3” and “non-M3” oversimplifies its genomic diversity. The FAB-based classification was intended to demonstrate the broad upregulation of MMRN1, not to provide a definitive subtyping framework. Interestingly, we did find that MMRN1 expression was significantly associated with NPM1 mutation status and cytogenetic risk in the TCGA database. As recently reported, Peng et al. identified MMRN1 as specifically upregulated in LSCs with the EGFR-mediated pathogenic mechanism, suggesting functional significance beyond specific co-mutations.[5] As a component of the validated LSC17 stemness signature, MMRN1 may capture stemness properties transcending mutational backgrounds.[7] Nonetheless, systematic investigation using patient-derived xenograft (PDX) models representing diverse molecular subgroups will be essential to illuminate MMRN1’s role in AML.

Finally, we thank Shen again for precisely identifying the directions for further investigation of this Mmrn1 research, which are exactly the avenues we are currently

planning to explore. We hope that these in-depth studies will provide more valuable reference information for clinical diagnosis and treatment.

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