Macro-scale, scaffold-assisted model of the human bone marrow endosteal niche using hiPSC-vascularized osteoblastic organoids

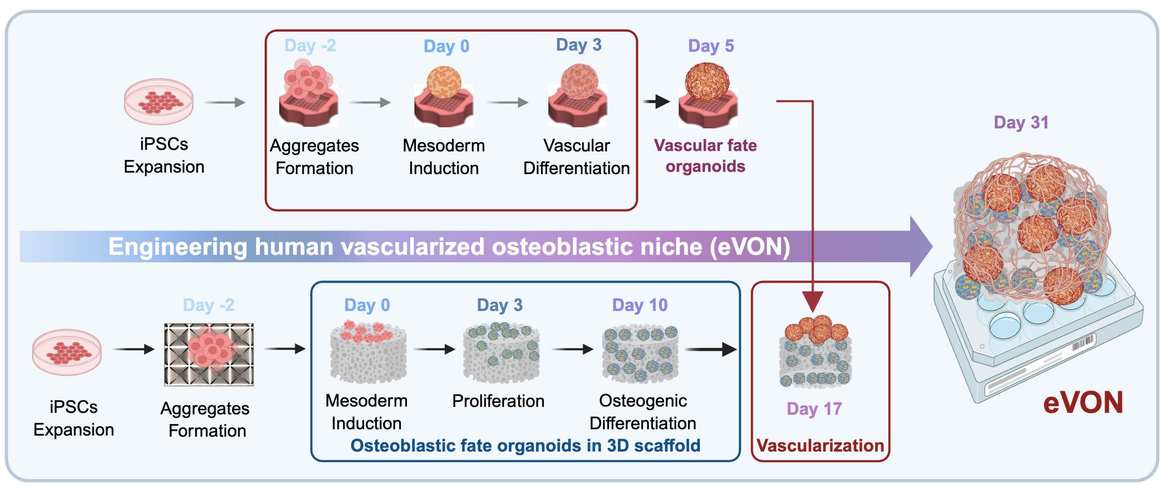
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ABSTRACT

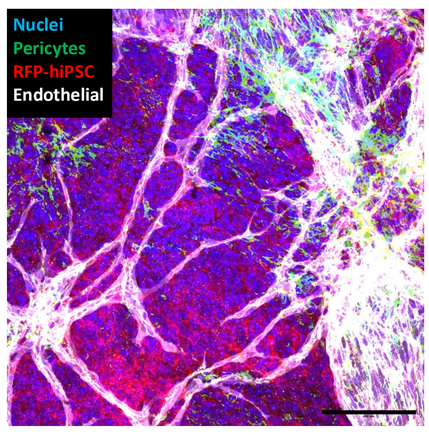
Endosteal bone marrow (BM) niches are crucial to sustain non-steady-state hematopoiesis but are challenging to be modeled in their cellular and molecular complexity in standardized, human settings. We report a developmentally guided approach to generate a macro-scale organotypic model of BM endosteal niches (engineered vascularized osteoblastic niche [eVON]) based on human induced pluripotent stem cells and porous hydroxyapatite scaffolds. The eVON contains long-lasting vascular networks covered by pericytes and neural fibers within an osteogenic matrix. Key niche signals (CXCL12, KITLG, and vascular endothelial growth factor A [VEGFA]) are expressed in human-specific patterns. The system supports hematopoiesis in vitro and preserves hematopoietic stem and progenitor cell (HSPC) multilineage repopulation capacity in vivo. eVON perturbations at cellular (removing vasculature) and molecular (deregulating VEGF-A and CXCL12 signaling) levels enabled the investigation of the contribution of endosteal vasculature to myelopoiesis. The eVON faithfully captures phenotypic, structural, and functional features of human endosteal BM, enabling the study of pathophysiological interactions with hematopoietic cells.

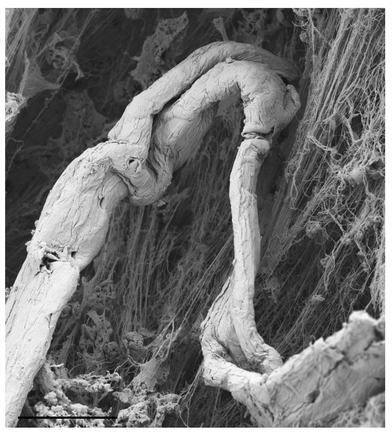
DESIGN

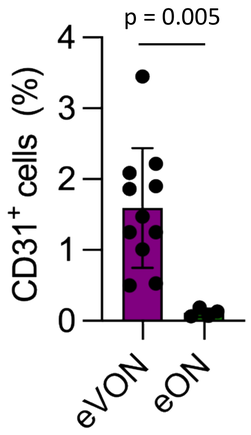


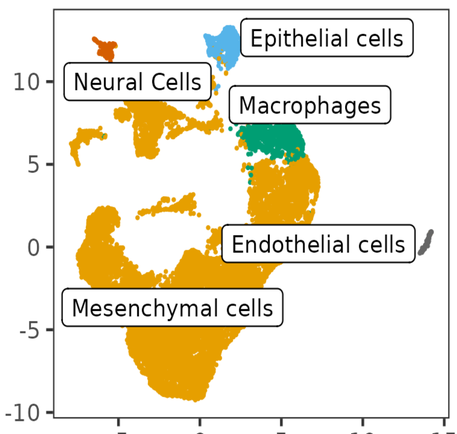
RESULTS

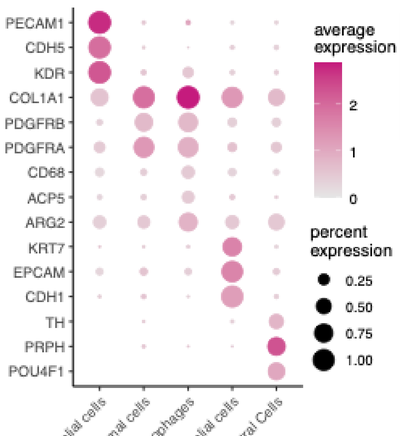
1. eVON recapitulates key features of human endosteal BM niches in xeno-free conditions

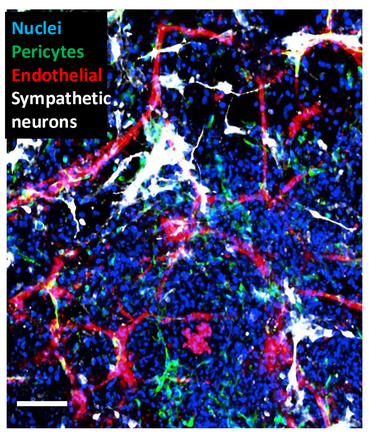


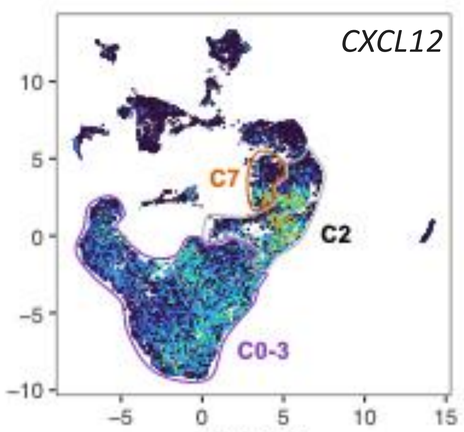


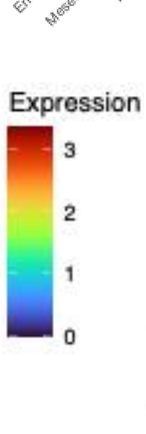


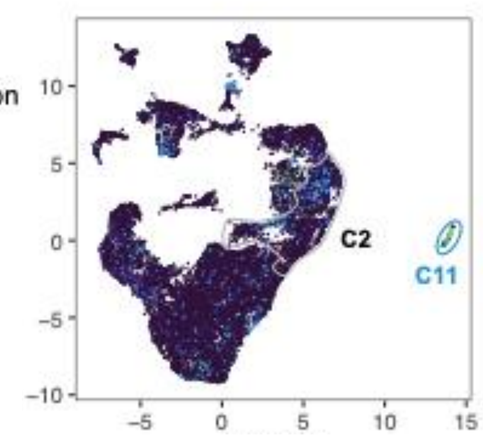


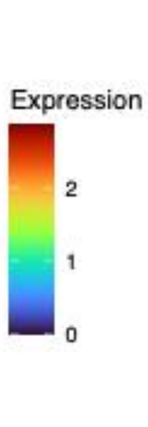






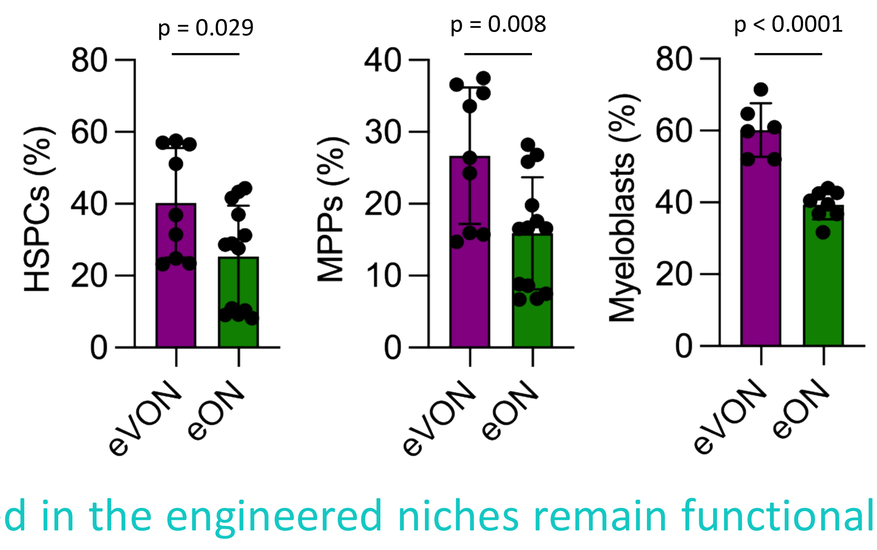




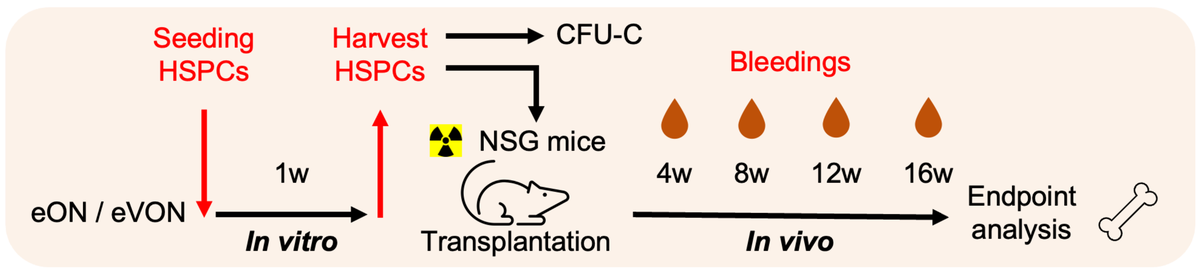


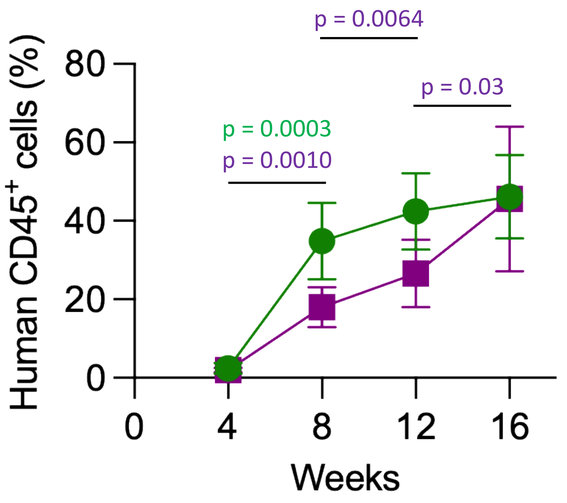
2. Endosteal vasculature enhances myelopoiesis in the eVON

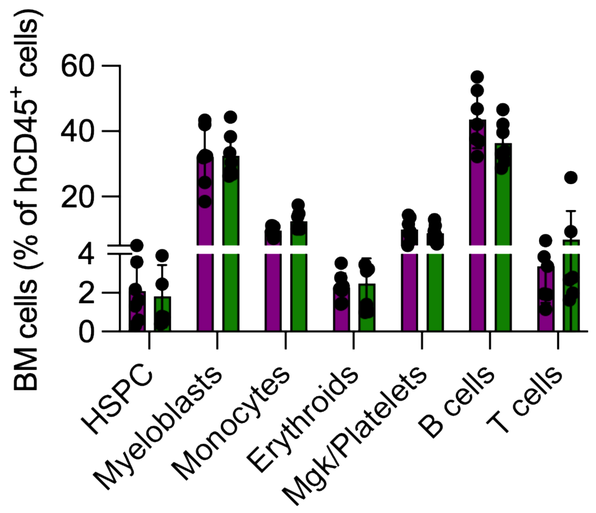




3. HSPCs cultured in the engineered niches remain functional and exhibit multilineage reconstitution *in vivo*







OUTLOOK

- Engineer patient-specific BM niches for personalized medicine
- Investigate the interactions between malignant hematopoietic cells and the endosteal niche
- Modeling solid tumor metastasis in bone

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