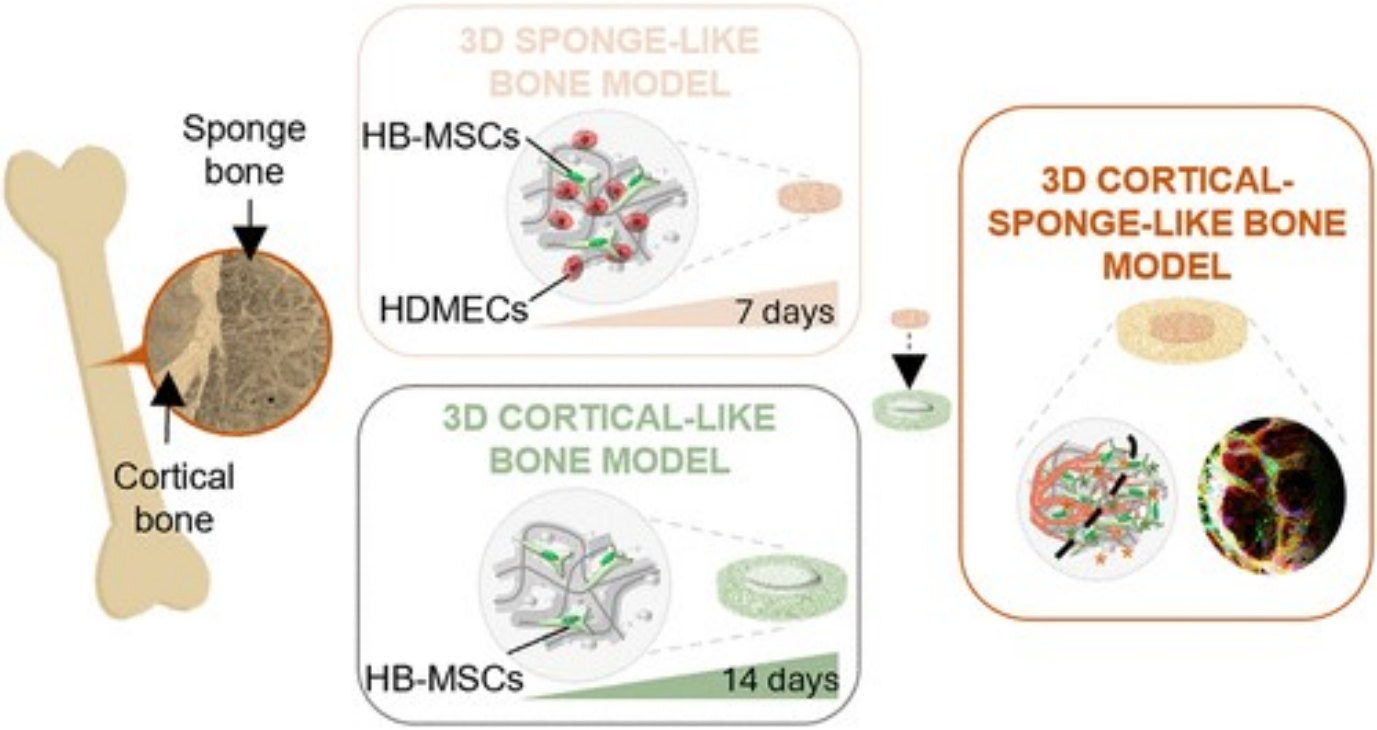
Bioinspired 3D Bone Model - Mimicking the Cortical–Spongy Bone Architecture and Biology for Enhanced Physiological Representation of Bone



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3D bone models are essential for studying bone physiology, developing therapies, and reducing animal use. Inspired by the hierarchical anatomy of the bone, we shaped previously developed gellan gum–hydroxyapatite spongy-like hydrogels into an outer ring and an inner disc to anatomically represent the cortical and spongy bone, respectively. Biomaterial properties remained stable postmolding, with the polymeric networks absorbing up to 500% of water and exhibiting 4 kPa stiffness. The outer ring was populated with human bone marrow mesenchymal stem cells (HBM-MSCs) and showed the expression of osteogenic genes (ALP/Runx-2/OPN/BSP) by day 14, with ALP and Runx-2 upregulated from day 7 ($p < 0.5$). Models also released angiogenic factors crucial for vasculogenesis, up to an average of 855 pg/mL VEGF, 38 pg/mL bFGF, and 2732 pg/mL Angiopoietin-1. The inner disc, loaded with HBM-MSCs and human dermal microvascular endothelial cells (HDMECs), formed tubular-like structures between days 7 and 14, along with the expression of endothelial cell-specific proteins (CD31/VE-cadherin/vWf) and extracellular matrix components (fibronectin/type I collagen). These effects may have been driven by the release of up to an average of 322 pg/mL VEGF, 243 pg/mL bFGF, and 184 pg/mL Angiopoietin-1. Constructs were then combined and cultured for an additional 7 days, showing a higher release of angiogenic factors in comparison to the independently cultured models, vasculature migration to the cortical-like part, and ALP expression in the spongy-like part. Overall, the 3D vascularized cortical-sponge-like model resembles the intricate cortical and spongy microarchitecture, offering a valuable platform for investigating bone (patho)physiology and potential therapies.