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Supporting Information

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Adaptable Hydrogels Mediate Cofactor-Assisted Activation of Biomarker-Responsive Drug Delivery via Positive Feedback for Enhanced Tissue Regeneration

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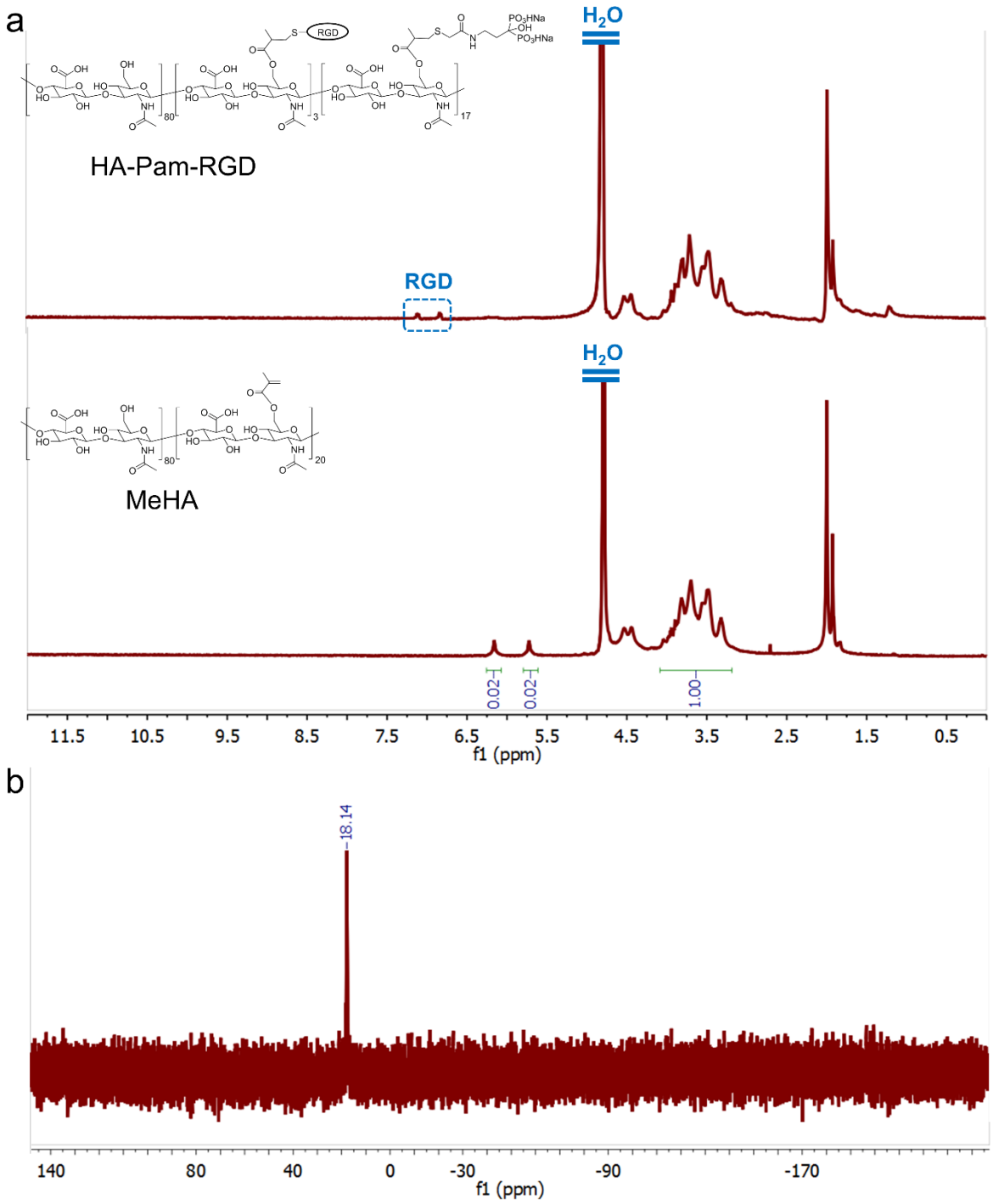

Figure S1. a) ^{1}H NMR spectra of MeHA and HA-Pam-RGD, indicating the complete consumption of the methacryloyl groups in MeHA. b) ^{31}P NMR spectrum of HA-Pam-RGD, confirming the successful conjugation of Pam to HA.

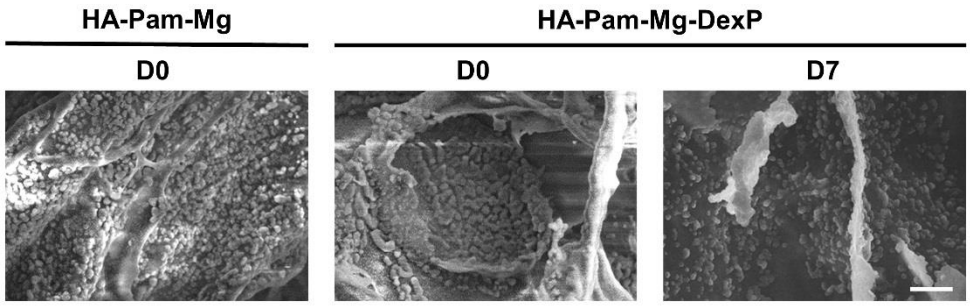

Figure S2. SEM images of the nanocomposite hydrogels; scale bar = 2.5 μm.

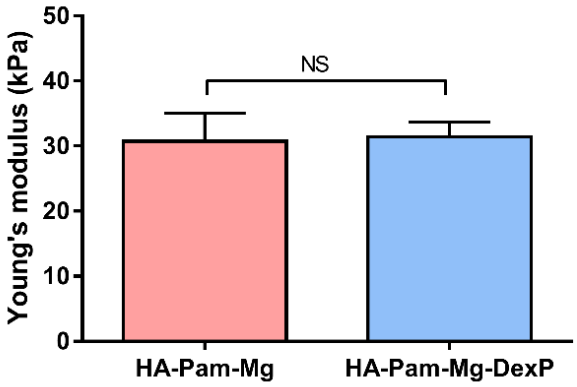

Figure S3. Average Young's modulus of unloaded and DexP-laden HA-Pam-Mg nanocomposite hydrogels. "NS" indicates no statistical significance ($P > 0.05$).

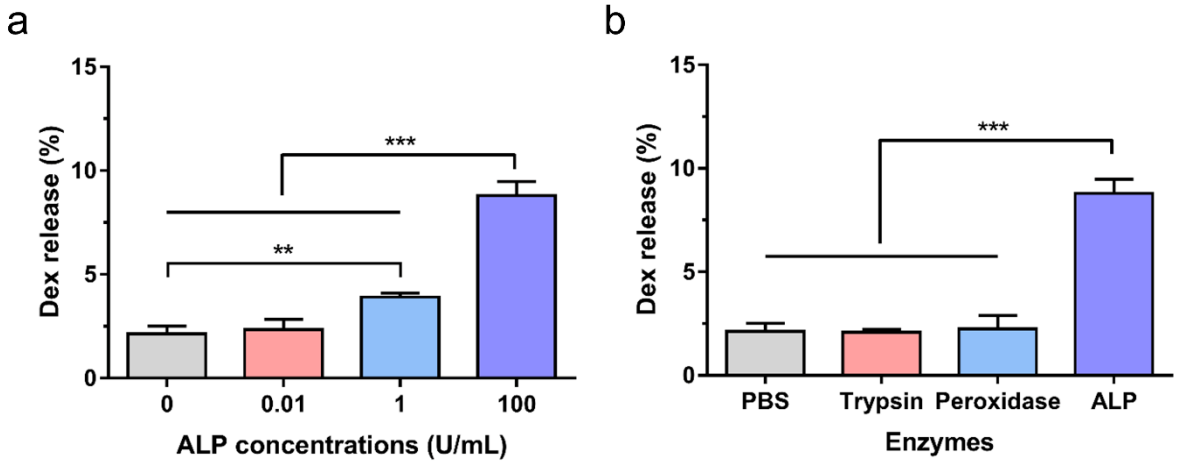

Figure S4. Dex release from the nanocomposite hydrogels after 24-hour incubation with a) various concentrations of ALP or b) various enzymes (100 U/mL). The DexP-laden hydrogels were pre-equilibrated in PBS for 3 days. $^{**}p < 0.01$, $^{***}p < 0.01$.

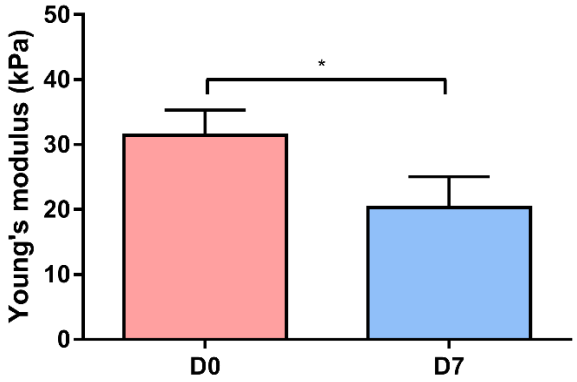

Figure S5. Average Young's modulus of the DexP-laden HA-Pam-Mg nanocomposite hydrogels before/after incubation in PBS for 7 days; $^{*}p < 0.05$.

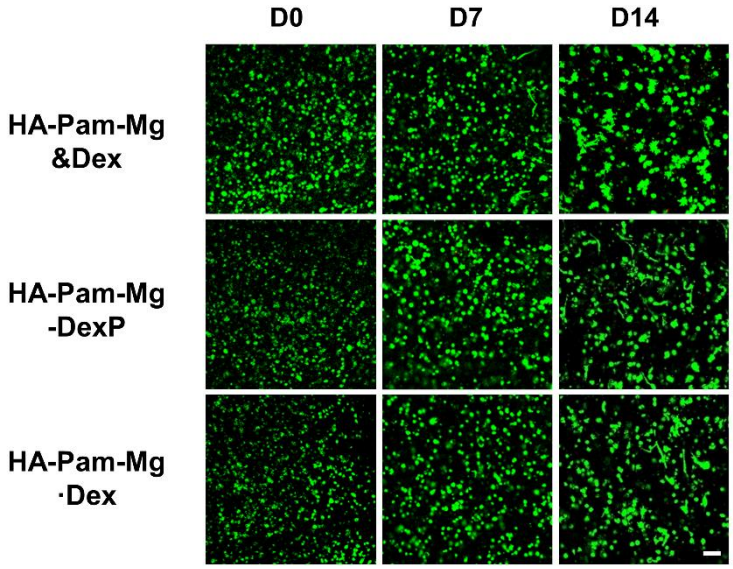

Figure S6. Live/dead staining (green: live, red: dead) of hMSCs encapsulated in the nanocomposite hydrogels; scale bar = 200 μm.

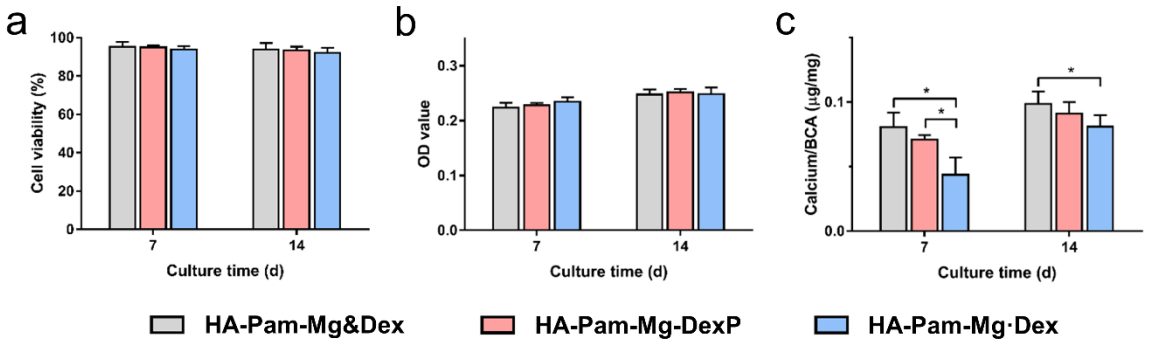

Figure S7. a) Cell viability of hMSCs encapsulated in the nanocomposite hydrogels as determined by live/dead staining. b) Alamar Blue assay showed that the encapsulated hMSCs exhibited similar levels of metabolic activity in all groups (n = 3). c) Calcium content of the cell-laden nanocomposite hydrogels (normalized to total protein content) (n = 3); $*p < 0.05$.

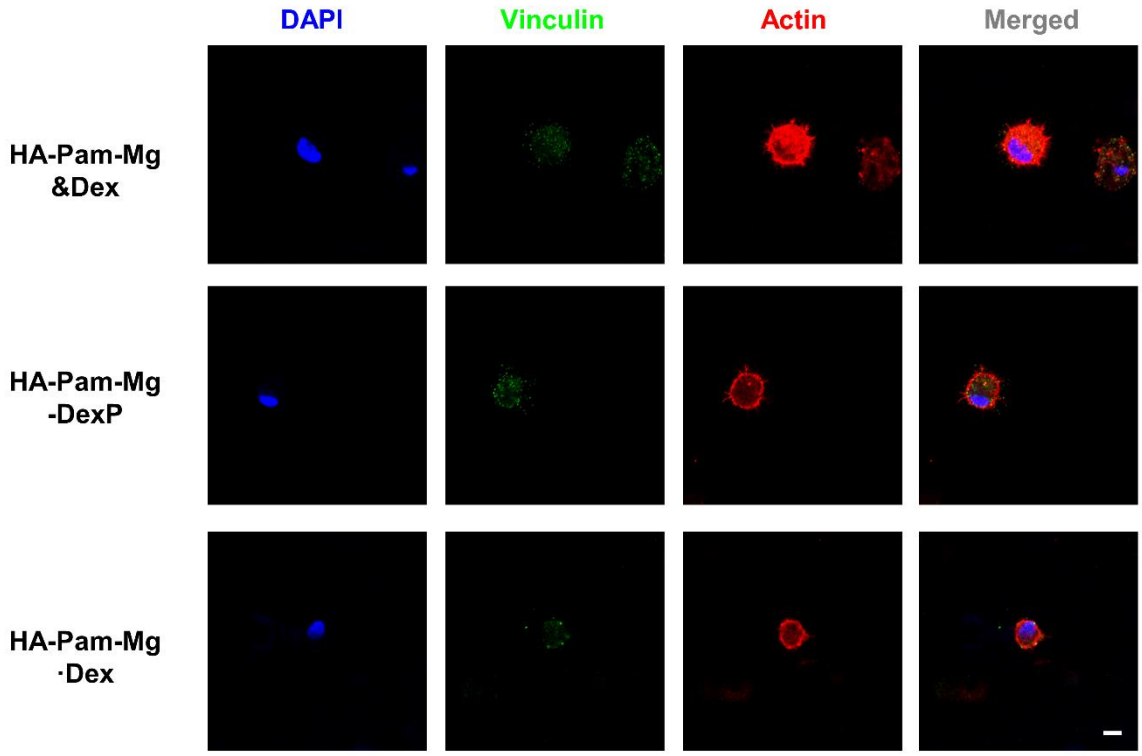

Figure S8. Fluorescent staining of hMSCs encapsulated in the 3D hydrogels after 7 days of osteogenic induction; scale bar = 10 μm.

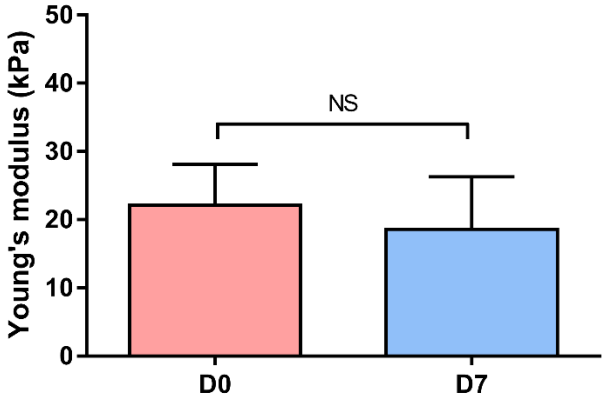

Figure S9. Average Young's modulus of the cell-laden hydrogels on Day 0 and Day 7 of culture. "NS" indicates no statistical significance ($P > 0.05$).

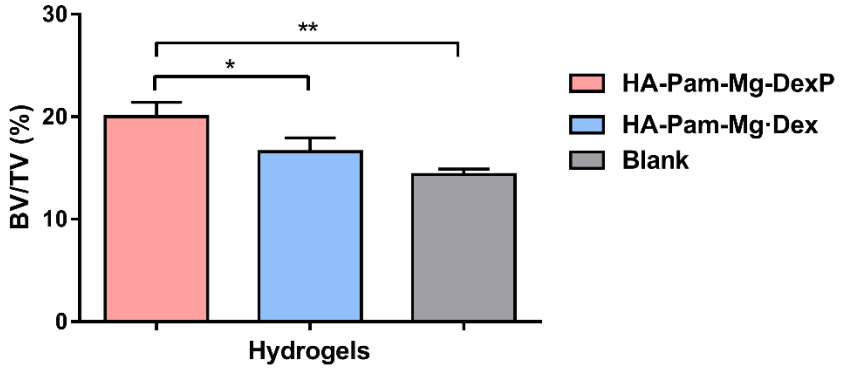

Figure S10. Quantitative bone volume analysis (BV: bone volume; TV: tissue volume) (n = 3); *$p < 0.05$, **$p < 0.01$.

Table S1. The sequence of the primers and probes used for real-time PCR is listed. The primer and probe sequences of the osteocalcin and Runx 2 are proprietary (Applied Biosystem) and not disclosed.

Gene	Forward primer	Reverse primer	Probe
GAPDH	AGGGCTGCTTTTA ACTCTGGTAAA	GAATTTGCCATGGG TGGAAT	CCTCAACTACATG GTTTAC
COL I	AGGACAAGAGGC ATGTCTGGTT	GGACATCAGGCGCA GGAA	TTCCAGTTCGAGT ATGGC
ALP	CGGAACTCCTGAC CCTTGAC	TGTTCAGCTCGTAC TGCATGTC	TCGAAGAGACCC AATAGGT