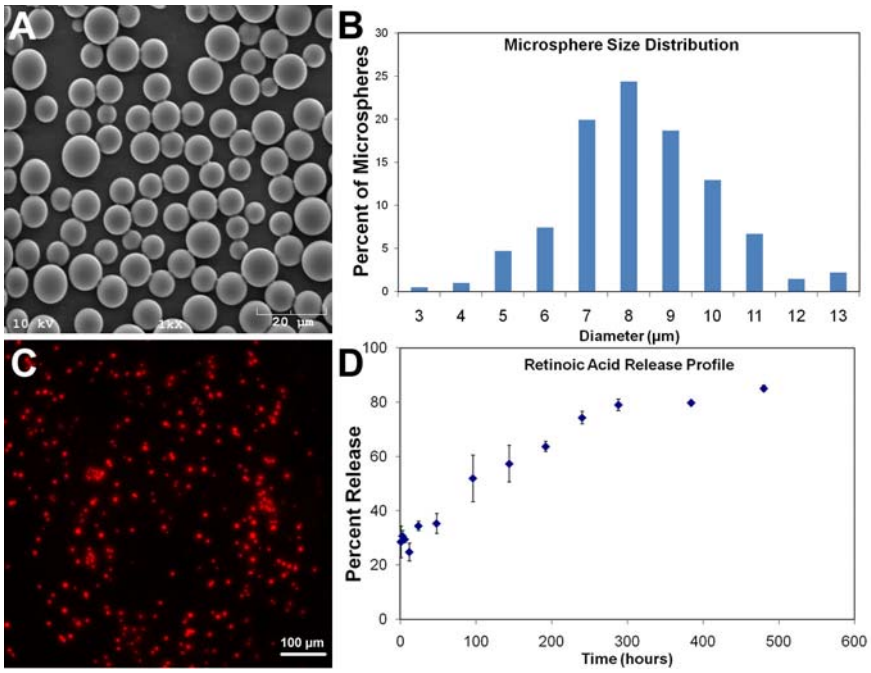
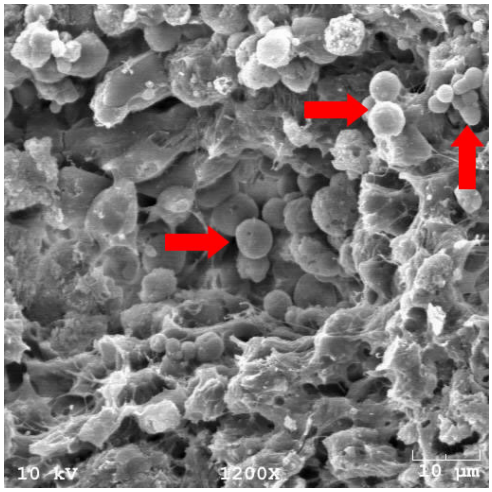
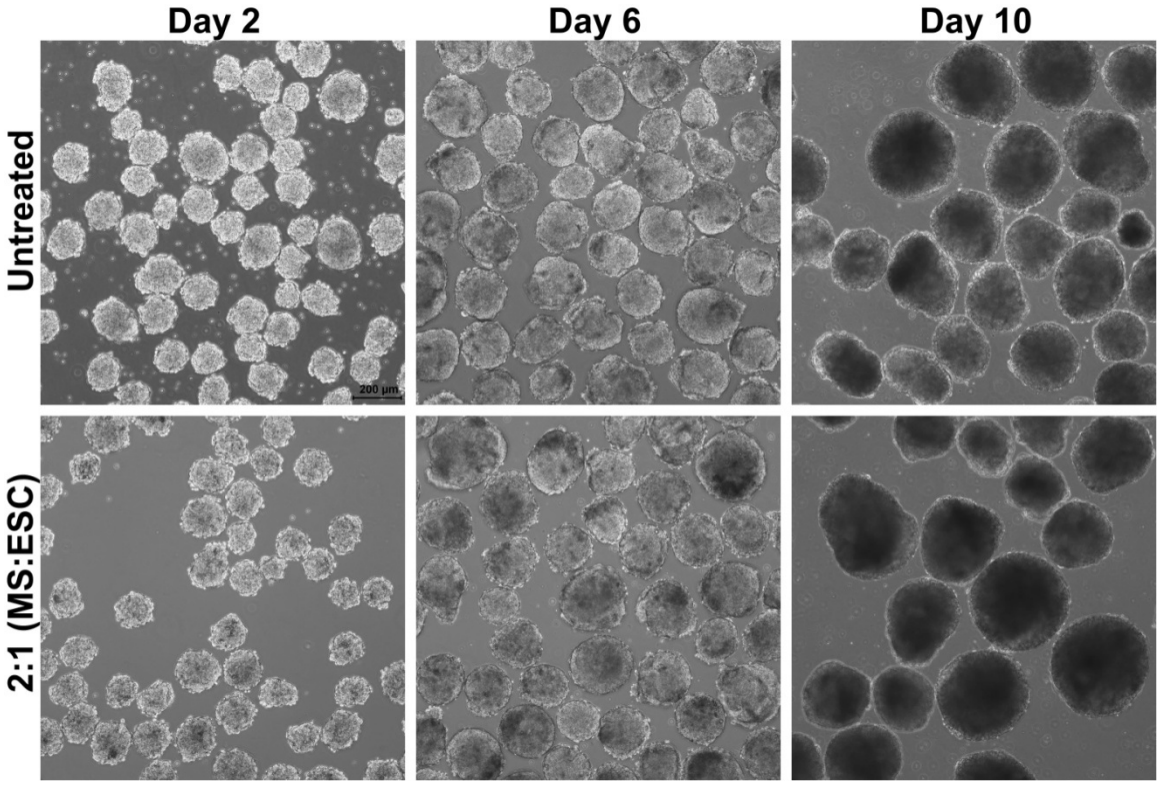


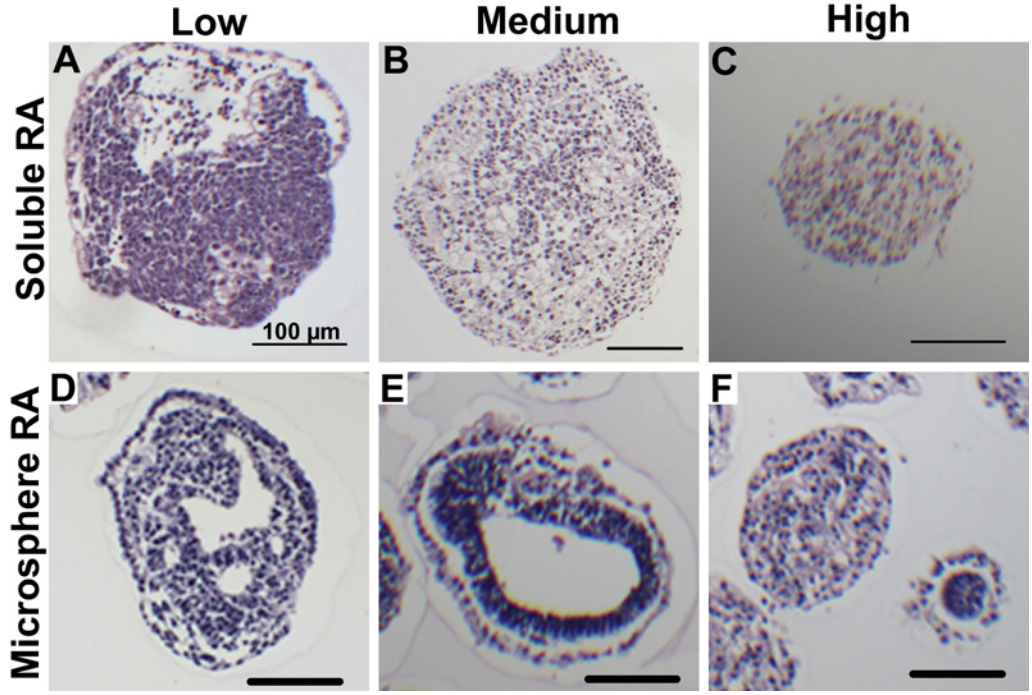
Supplemental Figure 1. Microspheres were fabricated using an oil-in-water emulsion and displayed smooth, spherical morphology in SEM micrographs (A). B) The size distribution was determined using image analysis of SEM micrographs, and the diameter was found to be 7.8 ± 1.8 µm (mean ± standard deviation). C) CellTracker Red™ was incorporated within microspheres allowing visualization with fluorescent microscopy. D) Release of RA from microspheres took place over the course of 14 days, and displayed a burst phase followed by sustained release.



Supplemental Figure 2. PLGA microspheres (red arrows) were visible in day 10 EBs formed from a 2:1 microsphere to cell ratio. EBs were bisected prior to imaging via SEM.

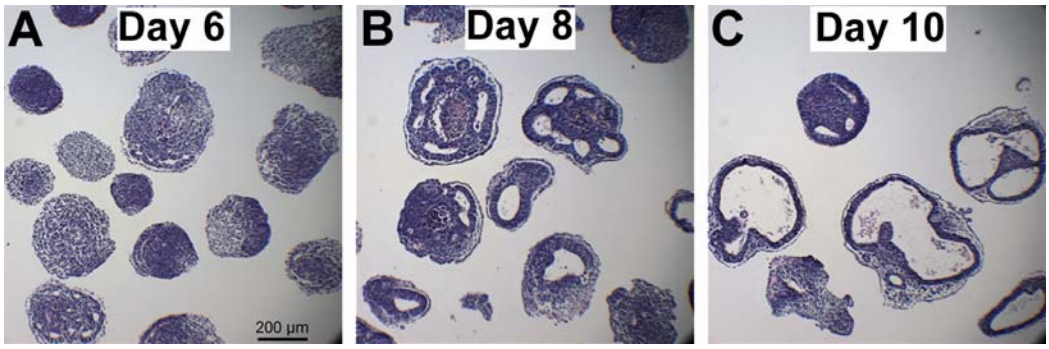


Supplemental Figure 3. EBs were formed at 40 rpm containing no microspheres or a 2:1 ratio of microspheres to cells. EB size and morphology appeared similar under both conditions after 2, 6 and 10 days of differentiation. Bar = 200 µm.



Supplemental Figure 4. Dose dependent response of EBs to RA. (A-C) Treatment of EBs with soluble RA with low (A, 0.01 µM) and medium (B, 0.1 µM) RA concentration results in solid spheroids after 10 days, while high RA (C, 10 µM) results in survival of few EBs and decreased EB size. (D-E) EBs containing microspheres with low RA concentration (D, 0.3 µg RA/mg

PLGA) induced formation of fewer cystic EBs and incomplete cystic regions compared to medium RA concentration (E, 3 µg RA/mg PLGA). EBs containing microspheres with high RA (F, 30 µg RA/mg PLGA) induced formation of small EBs with few cystic regions. All bars = 100 µm.



Supplemental Figure 5. Cystic EB formation. **(A)** Small cystic regions were visible in RA MS EBs after 6 days. (B) After 8 days, cysts appeared larger, and columnar cell layers become apparent. (C) By 10 days of differentiation, smaller cystic regions expanded and merged to form completely cystic EBs. Bar = 200 µm.