By removing immunogenic cells, tissue decellularization could turn off-the-shelf tissue scaffolds into viable means of treating patients with severe tissue damage. Despite numerous advances in tissue decellularization technology, donor-derived tissue scaffolds are plagued with microstructural damage and immunogenic contamination. This prevents decellularized tissues from being used clinically as tissue substitutes. To address this, we set out to develop a novel gene-based approach to tissue decellularization that uses a genetic switch (LTRi) to induce apoptosis in cells ultimately leading to decellularization. The results show that LTRi is able to control gene expression in embryonic stem (ES) cells and is therefore a viable means to control gene expression in terminally differentiated cells like those found in tissues being considered for replacement therapy. Furthermore, these results also demonstrate that gene control may be a feasible means of decellularization.