Programmable Non-replicating Mammalian Cells for Robust Biomanufacturing

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***Abstract*:**

Robust production of biologics and cell-derived nanoparticles is essential for modern medicine. Yet conventional biomanufacturing systems remain constrained by the dependence of biosynthesis on cell proliferation and survival. This coupling introduces tradeoffs between cellular fitness and production output, increasing variability, cost, and process complexity. Here, we engineer programmable non-replicating mammalian cells using our patented intracellular hydrogelation technology to create semi-living biosynthesis micromachines that sustain biomolecule production beyond the functional lifespan of natural cells. Intracellular polymer networks formed throughout the cytoplasm restrict replication while preserving metabolic activity, organelle integrity, and secretion capacity.

We demonstrate the utility of this platform across multiple bioproduct classes, including extracellular vesicles (EVs), lentiviral particles, and therapeutic antibodies. Engineered cells sustain EV secretion over extended culture periods compared to untreated controls and produce functional lentivirus with enhanced infectivity under stress conditions such as heat shock. Antibody secretion remains comparable to proliferative cells for up to seven days despite the absence of replication. By decoupling cellular survival from production, intracellular hydrogelation enables stable and parallelizable manufacturing workflows that are compatible with one-pot chemical modification, purification, and bioproduct stabilization strategies. Collectively, these findings establish engineered non-replicating cells as a versatile platform for next-generation biomanufacturing.

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