

COMMENTARY

Breast organoids: A paradigm shift from disease models to living pharmacies

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Abstract

Organoid technology has garnered significant attention for its ability to closely recapitulate the structure and function of parental tissues *in vitro*. Over the past decade, this technology has primarily served as a passive disease model widely applied in drug screening and precision medicine. Transforming these static *in vitro* models into dynamic therapeutic tools remains a critical bottleneck in the field. Bridging this gap requires shifting from merely simulating diseases to actively repairing tissues. Recently, a groundbreaking study published in *Nature Biomedical Engineering* introduced an innovative “living pharmacy” strategy—engineered organoids that function as autonomous, implantable drug factories capable of sustained local drug production and tissue regeneration—using engineered breast organoids. This approach transcends previous limitations and offers a promising solution for postoperative breast cancer treatment and breast function regeneration.

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Organoid technology reconstructs the cellular heterogeneity, spatial architecture, and key functions of native tissues in three dimensions. It has become a vital platform that addresses the insufficient translational predictability of conventional models.¹ However, its clinical application in tumor therapy remains constrained by limited functional diversity and a heavy reliance on biomaterials for delivery systems.^{2,3} For a long time, patient-derived tumor organoids have served primarily as static models for *in vitro* surrogate drug testing. The distinction between these “screening organoids” and the emerging “therapeutic organoids” is fundamental: the former are passive tools for observation, while the latter are active agents designed to intervene and repair. The transition from one to the other faces two major hurdles—how to endow organoids with therapeutic effector functions beyond simple cytotoxicity, and how to achieve controlled delivery without exogenous scaffolds. Current research frontiers are now addressing these bottlenecks through two main approaches. First, functional expansion moves beyond traditional drug testing. Researchers are engineering organoids into active

therapeutic units or complex simulation platforms. For instance, scientists now use organoids to evaluate the safety and efficacy of novel nanomedicines, such as hydrophilic molybdenum disulfide.⁴ A more radical approach involves transplanting CRISPR-engineered brown adipose organoids adjacent to tumors. These implants competitively deplete nutrients to inhibit tumor growth, transforming the role of organoids from mere disease models into transplantable metabolic therapeutic devices.⁵ Second, delivery systems are reducing their dependence on exogenous scaffolds. The focus is shifting toward intelligent biological carriers with higher biocompatibility and precise targeting. In gastric cancer treatment, engineered small extracellular vesicles derived from natural killer cells serve as nanocarriers. They demonstrate accurate tumor targeting and radio-sensitizing effects.⁶ Similarly, aptamer-functionalized engineered exosome delivery systems for colorectal cancer show robust targeting and anti-tumor efficacy in both organoid and *in vivo* models.⁷ This indicates a shift in organoid transplantation and drug delivery toward utilizing engineered natural biological carriers. The goal is to achieve superior biointegration and precise spatiotemporal control. Despite these advances, organoid technology still faces core challenges. The recapitulation of the tumor microenvironment remains incomplete. Current culture methodologies continue to rely on animal-derived matrix gels to varying degrees. Furthermore, standardized protocols for culture and drug sensitivity assessment are lacking. These factors collectively impede clinical translation.⁸

To address these challenges, the research team led by Zhen Gu established a novel pathway.⁹ Instead of modifying exogenous materials, they reprogrammed the endogenous lactation program of breast organoids. This transformation turned the organoids into autonomous biological systems capable of integrating drug loading, on-demand release, and tissue repair (Figure 1A). The core mechanism lies in the lactation-induced intracellular accumulation of lipid droplets, which serve as natural depots for hydrophobic prodrugs. The researchers synthesized a prodrug by linking all-trans-retinal (ATRA) and doxorubicin (DOX) via an acid-sensitive linker. This hydrophobic prodrug loads efficiently into the lipid droplets with a capacity reaching 85.3% (Figure 1B and 1C). Upon implantation into the surgical cavity, myoepithelial cells within the organoids continuously secrete the drug-loaded lipid droplets into the surrounding microenvironment through contraction—a process that closely mimics physiological lactation. Importantly, the acidic microenvironment created by residual tumor cells specifically activates the prodrug and releases active DOX, enabling spatially targeted drug delivery and localized activation while

minimizing systemic toxicity (Figure 1D). This design merges cell biology with stimuli-responsive materials chemistry, achieving both passive storage and active, physiologically triggered release.

This strategy demonstrated notable dual efficacy in a mouse model of postoperative breast cancer. A single implantation of the engineered organoids achieved a 96% tumor regression rate and significantly inhibited recurrence (Figure 1E). The therapeutic mechanism extends beyond direct chemical cytotoxicity. Local release of DOX induces immunogenic cell death at the tumor site, while the ATRA moiety acts synergistically to modulate the tumor microenvironment (Figure 1F). The regenerative outcomes showed even more impressive advancements. The implanted organoids successfully engrafted and integrated into the host mammary fat pad to drive the formation of new ductal and acinar structures. Furthermore, these organoids restored lactation function in recipient mice during subsequent pregnancies (Figure 1G). This represents a critical leap from structural regeneration to functional regeneration. The quality of this biological repair substantially exceeds that achieved by passively filling the cavity with inert scaffold materials.

Harnessing this synergy between physiological secretion and pathological triggers endows the platform with distinct advantages over alternative delivery modalities. Whereas cell therapies are often constrained by limited graft persistence and complex ex vivo manipulation, and engineered extracellular vesicles face inherent barriers in payload capacity and *in vivo* stability, the organoid-based living pharmacy uniquely consolidates drug synthesis, storage, and on-demand delivery within a single, self-perpetuating biological unit. Critically, this integrated design aligns seamlessly with the dual clinical objectives of tumor suppression and functional gland restoration.

The platform also demonstrated promising translational potential from murine to human sources. The research team derived human breast organoids from human induced pluripotent stem cells. Applying the same engineering protocol, they validated the robust tumor-suppressive and tissue-integrative capabilities of these human organoids in immunodeficient mouse models (Figure 1H and 1I). This success establishes a solid mechanistic foundation for future personalized clinical translation.

Collectively, this work fundamentally redefines the pivotal role of organoid technology across three transformative dimensions. First, it shifts the scientific paradigm from passive observation of disease to active therapeutic intervention. Second, it transitions the physical construct from an exogenous, scaffold-dependent implant to an endogenous, integrated, self-sustaining living repair

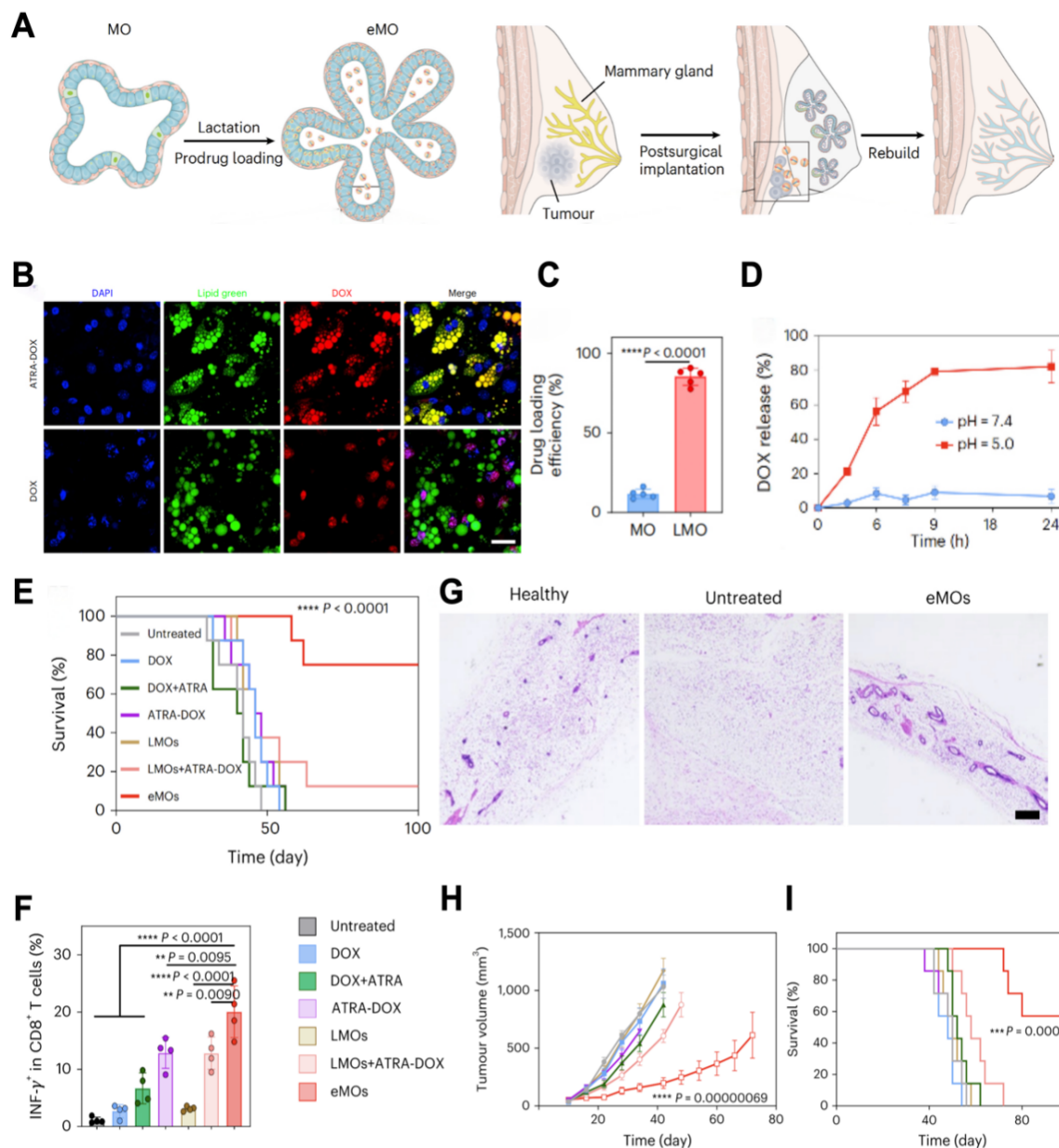


Figure 1. Engineered mammary organoids (eMOs) for postoperative therapy and regeneration. (A) Schematic of eMO generation via lactation induction and implantation into the surgical cavity. (B) Confocal images showing colocalization of the prodrug (green) and lipid droplets (red); nuclei (blue). (C) Cell viability of MOs, eMOs, and free DOX treatment. (D) Acid-triggered prodrug release kinetics at pH 7.4 vs. 5.0. (E–F) eMOs improve survival (E) and enhance intratumoral IFN- γ^+ cells (F) in orthotopic models. (G) Hematoxylin and eosin staining showing restored glandular architecture in eMO-treated mice. (H–I) eMOs suppress tumor growth (H) and extend survival in humanized xenograft models (I). Abbreviations: ATRA: All-trans retinal; DAPI: 4',6-diamidino-2-phenylindole; DOX: Doxorubicin; eMO: Engineered mammary organoid; IFN- γ : Interferon gamma; LMO: Lactation-induced mammary organoid; MO: Mammary organoid.

unit. Third, it expands the utility of organoids from a conventional *in vitro* screening tool to a sophisticated, implantable, *in vivo* customizable bioreactor platform. By ingeniously harnessing organ-specific secretory pathways for precise, targeted molecular delivery, this innovative strategy establishes a universal and adaptable paradigm for regenerating complex secretory organs, such as the salivary glands and the pancreas (Figure 2). It should be

noted, however, that such extrapolations remain to be experimentally validated in each target tissue, given the distinct developmental and secretory programs of different organs. At the same time, the path to clinical translation requires careful consideration of long-term cellular viability, immune compatibility, and manufacturing scalability under Good Manufacturing Practice standards.^{10,11}

In summary, this study bridges developmental

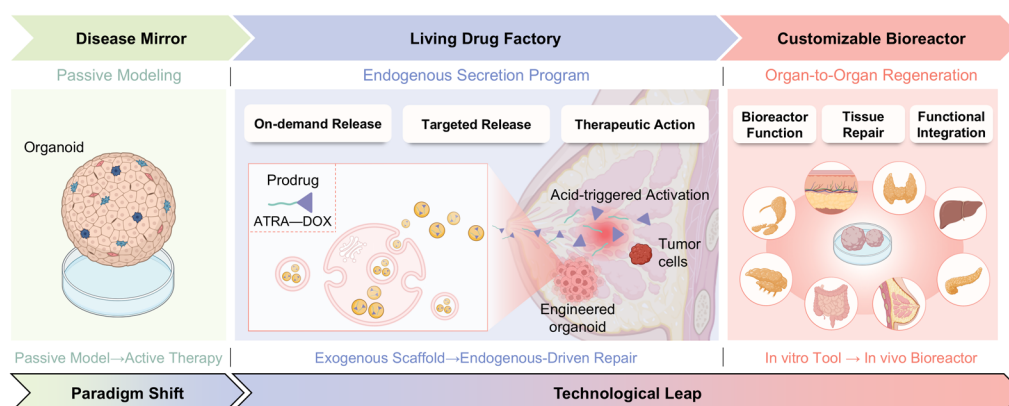


Figure 2. The concept of organoids has shifted from passive disease modeling to active therapeutic bioreactors

biology, synthetic chemistry, and biomaterials science. It successfully transitions organoids from a laboratory observation tool to a clinical therapeutic frontier. The research provides revolutionary concepts for the comprehensive postoperative treatment of breast cancer. By fundamentally reshaping the application paradigm of organoid technology, this work heralds a new era in regenerative medicine where biological constructs are used directly to repair and treat organs.

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Conflict of interest

The authors declare no competing interests.

Author contributions

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Ethics approval and consent to participate

Not applicable.

Consent for publication

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