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Global landscape of organoid biobanks: Bibliometric insights, technological breakthroughs, and clinical translation

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Abstract

Organoid biobanks represent a pivotal innovation at the intersection of stem cell biology, bioengineering, and precision medicine. By establishing standardized repositories of patient-derived organoids spanning diverse tissues and disease contexts, organoid biobanks enhance experimental reproducibility, foster international scientific collaboration, and accelerate translational research. This study presents a comprehensive bibliometric analysis of 1,318 publications over the past three decades and identifies transformative shifts in the field. Research output has increased substantially since 2014, driven by international consortia involving institutions in China, the United States, and Europe. The analysis highlights predominant applications in cancer modeling (particularly gastrointestinal and central nervous system malignancies), high-throughput drug screening, and regenerative medicine, with emerging frontiers in multi-organ system integration and artificial intelligence-enabled predictive modeling. Technological advances are increasingly being evaluated for clinical relevance through reported concordance between organoid-based predictions and patient treatment responses. While challenges persist in the functional maturation of organoids and in ethical governance, organoid biobanks are increasingly positioned to reshape biomedical research paradigms by bridging experimental models with clinical decision-making. The strategic development of standardized protocols and interdisciplinary frameworks will be essential to realize their full potential in advancing therapeutic discovery and personalized healthcare.

Keywords: Organoid biobanking; Patient-derived organoids; Disease modeling; Translational medicine; Multi-omics integration

1. Introduction: The organoid revolution and a paradigm shift in biobanking

Organoid technology represents a paradigmatic advance in contemporary biomedical research by enabling three-dimensional (3D) *in vitro* culture systems that faithfully recapitulate the spatiotemporal dynamics of organogenesis.[1–4] Compared with conventional two-dimensional (2D) cell models, organoids derived from pluripotent stem cells or tissue-resident progenitors achieve systems-level reconstitution of the organ of origin across both spatial architecture (e.g., cortical lamination) and physiological function (e.g., intestinal epithelial barrier function and metabolism).[5–7] This biomimetic fidelity transcends the traditional constraints of cell culture and provides an indispensable platform for elucidating disease mechanisms, profiling drug responses, and advancing personalized medicine.[7,8]

The field of organoid research was shaped by a series of paradigm-defining breakthroughs that established the core principle of intrinsic self-organization for 3D tissue reconstruction. In 2009, Sato *et al.*[9] first demonstrated that single LGR5$^+$ intestinal stem cells could autonomously assemble into crypt-villus structures *in vitro* without a mesenchymal niche, laying the foundational technical framework for adult stem cell-derived organoid systems.[9] Shortly thereafter, Eiraku *et al.*[10] achieved de novo generation of stratified 3D optic cups from mouse embryonic stem cells in 2011, faithfully recapitulating retinal morphogenesis and proving that complex organ developmental programs could be fully reconstituted *ex vivo*. In 2013, two transformative studies further expanded the scope and translational potential of the field. Lancaster *et al.*[6] developed cerebral organoids that modeled human fetal brain development and recapitulated microcephaly pathogenesis, while Takebe *et al.*[11] generated vascularized functional liver buds from human induced pluripotent stem cells (iPSCs) that could engraft and exert metabolic activity *in vivo*. Building on these foundational advances, the repertoire of organoid models has expanded steadily over the past two decades—from neural crest-derived lineages to pancreatic endocrine tissues—propelling a transition from fundamental developmental biology to clinically oriented translational medicine.[12–14]

The evolution of biobanking has been fundamentally transformed by the advent of organoid technology.[15,16] Whereas early biobanks (as defined by the Organisation for Economic Co-operation and Development) primarily stored static biological materials, organoid biobanks preserve viable functional units that exhibit sustained self-renewal and directed differentiation capabilities.[17] By systematically integrating high-fidelity disease models spanning colorectal and gastric cancers, gliomas, and additional indications, these repositories have established a dynamic, multi-organ network of biological resources (Figure 1A).[13,18,19] This transformation not only preserves the standardized governance frameworks of traditional biobanking but also preserves the pathophysiological properties of organoids, thereby catalyzing a qualitative shift from a passive "biological archive" to an active "functional system." In 2016, the Human Proteome Organization formally recognized organoid resources as core research infrastructure, underscoring their strategic importance in advancing precision medicine.[20]

The core value of organoid biobanks manifests in three interrelated dimensions: (i) standardization to ensure cross-platform reproducibility, (ii) scalability to enable global collaboration, and (iii) clinical relevance to inform precision decision-making.[20,21] On the standardization front, optimization of cryopreservation and recovery protocols (e.g., vitrification-based methods) and rigorous quality-control metrics (e.g., genetic stability assays) substantially enhance interlaboratory comparability. Regarding scalability, a global ecosystem of mature, publicly accessible organoid biobanks has been established to support resource sharing and collaborative research. The HUB Organoid platform, originating from the Hubrecht Institute and the University Medical Center Utrecht as the pioneering large-scale patient-derived organoid (PDO) repository, has distributed thousands of tumor and normal organoid models across hundreds of laboratories worldwide, markedly reducing redundant research-and-development expenditures.[17] Complementing this European infrastructure, the Human Cancer Models Initiative (HCMI)—an international consortium led by the United States National Cancer Institute, American Type Culture Collection (ATCC), the Wellcome Sanger Institute, and the Broad Institute—curates a systematically standardized collection of cancer organoids paired with full clinical annotations and multi-omic profiling data, all openly available to the global research community via the ATCC platform.[22] The Wellcome Sanger Institute Tumor Organoid Biobank, as a core contributing partner of HCMI, further maintains a high-quality multi-cancer organoid cohort integrated with deep genomic and pharmacophenotypic datasets, enabling large-scale drug screening and mechanistic dissection of tumor heterogeneity.[23] These well-established biobanking resources collectively form the backbone of global organoid research collaboration. Clinically, PDOs retain patient-specific pathological features, rendering them pivotal for the prediction of chemotherapy sensitivity (e.g., gastric cancer PDOs exhibit approximately a 78% concordance with clinical outcomes) and for validating gene-editing-based therapeutic strategies.[7,24,25] Current frontiers—including high-throughput drug screening, integration with multi-

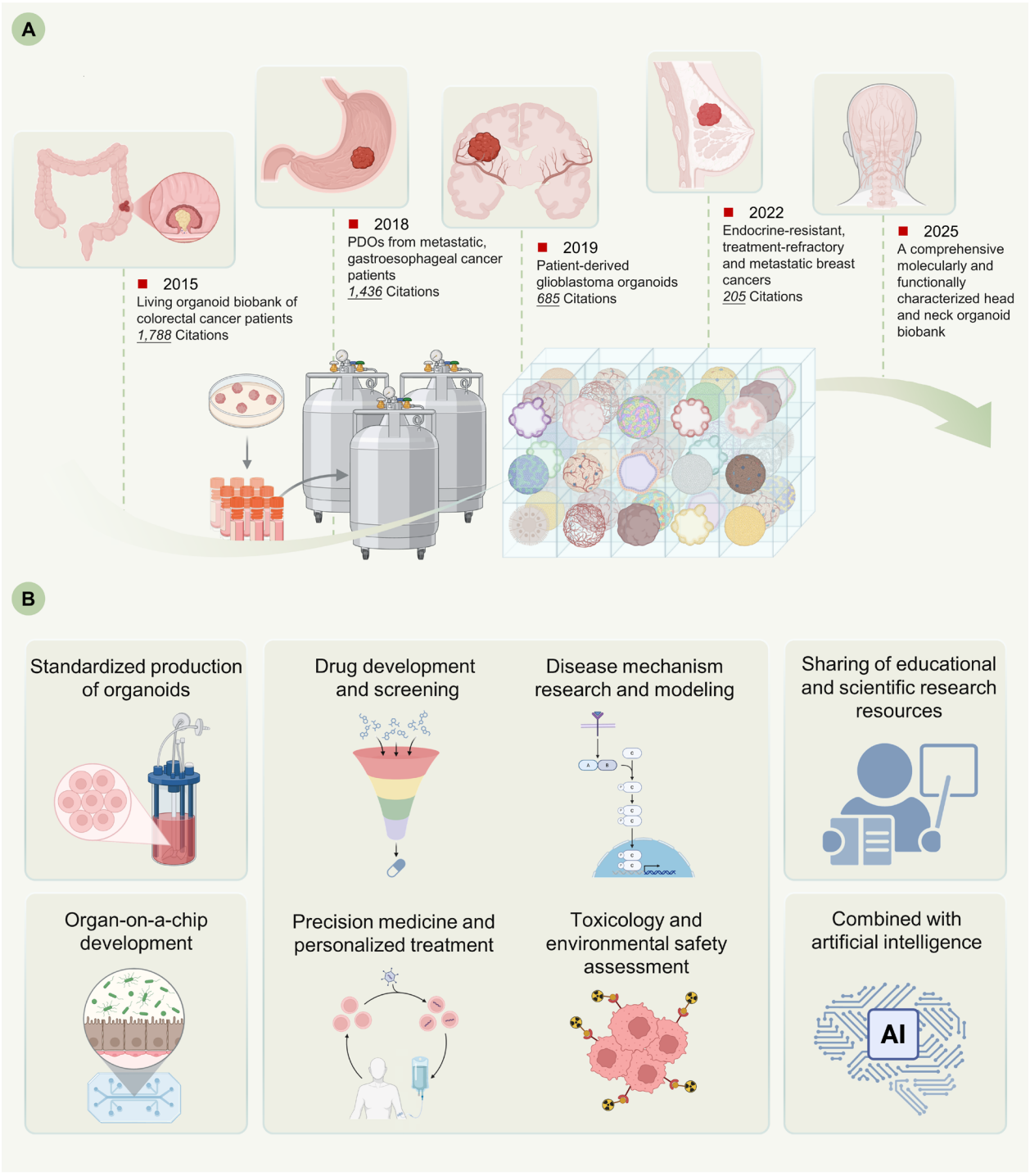

Figure 1. Overview of organoid biobanking technologies. (A) Development of organoid biobank: Over the past decade, organoid biobanks have expanded rapidly, establishing well-characterized, disease-specific repositories for colorectal and gastric cancers, gliomas, breast cancer, and head and neck malignancies. (B) Application scenarios for organoid biobank: Organoid biobanks underpin key applications, including drug discovery and high-throughput screening, disease modeling, and precision medicine, while also serving as versatile platforms for education and research. Created in BioRender. Liu, J. (2026). https://BioRender.com/dty6uw0.

organ-on-a-chip systems, and artificial intelligence (AI)-driven analytics (Figure 1B)—further position organoid biobanks as hubs of translational medicine.[26,27] Using bibliometric methods, this study systematically maps the field's evolutionary trajectory and technological inflection points.[28]

2. Global research landscape: A comprehensive bibliometric analysis of organoid biobanking

2.1. Bibliometric methods

A structured literature search was conducted in the Web of Science Core Collection and PubMed to characterize the research landscape and temporal evolution of organoid-related studies (Figure 2).[28] The topic search query was as follows: TS=(organoid OR organoids OR mini-organ OR "tissue culture model" OR "in vitro organ" OR "3D cell culture" OR "organotypic culture" OR microtissue) AND TS=(biobank OR database OR bio-bank OR biorepository OR biocollections OR "biological sample bank" OR "tissue bank").[29]

The search included the following document types: original research articles, reviews, letters, meeting abstracts, and editorial material relevant to the topic.[30] Records retrieved from both databases were exported in their original formats and merged into a single dataset. Cross-database deduplication was then performed using DOI, PMID, and title–year matching. After deduplication, 1,318 unique publications were retained for the final bibliometric analysis.[31]

To comprehensively characterize the field and its developmental trajectory, we performed multi-dimensional bibliometric analyses and visualized the distribution and relationships of contributions across countries and regions, institutions, authors, journals, keywords, and disease-related topics.[32] VOSviewer (version 1.6.18, Centre for Science and Technology Studies, Leiden University, The Netherlands), Pajek (version 5.16, 64-bit, University of Ljubljana, Slovenia), and SCImago Graphica (version 1.0.35, SCImago Research Group, Spain) were employed to visualize co-occurrence relationships across these dimensions. CiteSpace (version 6.3.R1, developed by Chaomei Chen, USA) was used to construct co-citation networks and keyword-based knowledge maps, thereby supporting the identification of intellectual structure and evolving research hotspots.[33,34]

In addition, journal-level analyses, including productivity–impact distributions, time-overlay visualizations, and co-citation patterns, were used to assess the publication landscape of the field.[34,35] To further illustrate temporal changes in thematic emphasis, annual keyword heatmaps, keyword timeline bubble plots, and theme river plots were generated based on the deduplicated

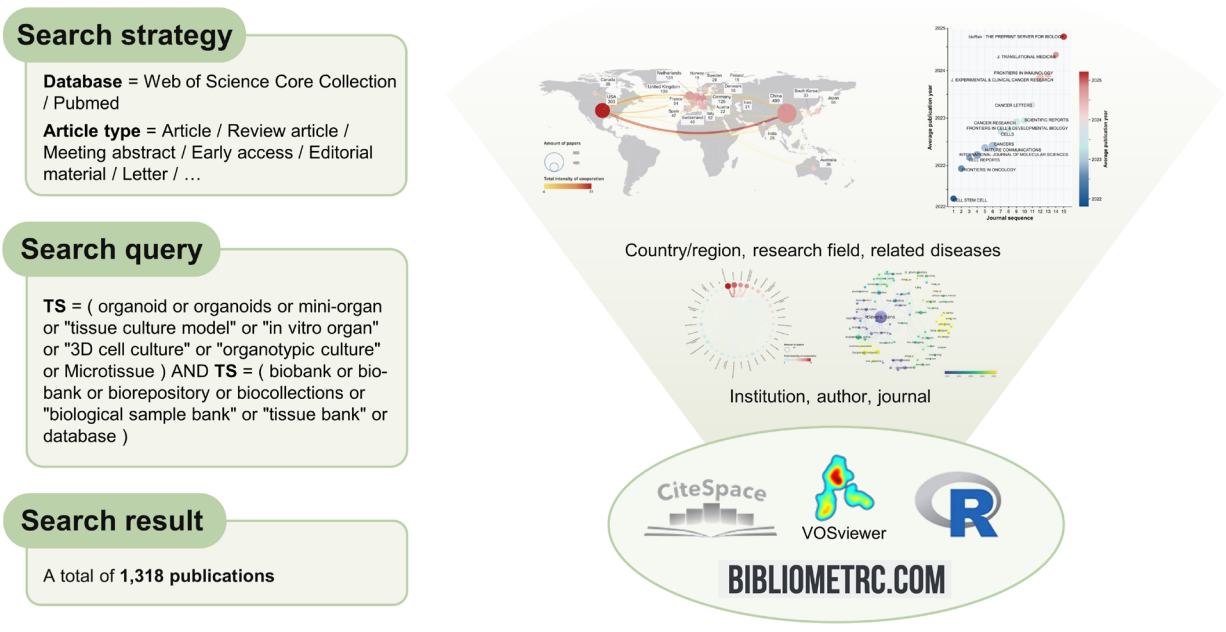

Figure 2. Schematic overview of the bibliometric analysis pipeline for the organoid biobanking research domain

dataset; the heatmaps were produced using the R packages ComplexHeatmap (version 2.16.0, Zuguang Gu, Germany) and circlize (version 0.4.15, Zuguang Gu, Germany).[36,37] Collectively, these visual analytics delineate the global landscape of organoid-related research, identify major contributors and collaboration patterns, reveal core publication venues and knowledge bases, and clarify the temporal evolution of thematic directions and disease-oriented applications.[32,38]

Notably, retrieval relied solely on metadata (e.g., title, abstract, keywords, MeSH/Keywords Plus) instead of full-text extraction. Metadata-based searching ensures high reproducibility and avoids restrictions associated with journal access and text-mining copyright limitations.[39] Although metadata-based retrieval avoids major biases brought by full-text mining, multiple residual selection biases remain inherent to this scheme, which we have counteracted via two complementary mitigation strategies. First, cross-verification between Web of Science and PubMed offsets Open Access (OA) overrepresentation bias: OA journals often receive more complete and timely abstract indexing, which may inflate their proportional share in raw retrieval outcomes. The dual-database design balances this flaw, as Web of Science covers a large number of subscription journals while PubMed delivers policy-backed wide literature coverage, thereby compensating for each platform's individual indexing limitations. Second, parallel retrieval of the two databases reduces systematic coverage bias. Distinct journal inclusion standards and paywall restrictions cause each database to underrepresent certain subscription journals; joint searching reduces the systemic loss of paywalled periodical records.

2.2 Research trajectories and scholarly impact

2.2.1. Field trajectory: Sustained expansion in annual publication output

Since the first indexed record in 1994, research on organoid biobanking has shown marked and sustained growth. Annual publication output increased from three articles in 1994 to 310 in 2025, with a cumulative total of 1,318 publications, attesting to the steady intensification of scholarly attention and research momentum.

A marked inflection point emerged in 2018, with annual publications rising from 10 in 2017 to 30 in 2018, equivalent to a year-on-year growth rate of 200.00%. The upward trend persisted in 2019, when the publication count increased to 56, corresponding to an additional 86.67% increase (Figure 3A).[32,33,35] This sustained acceleration suggests that organoid biobanking began to gain substantial momentum after 2018 and progressively established itself as an increasingly important area of biomedical research.

2.2.2. International collaboration and national influence: Regional clustering and core leadership

Bibliometric visualization reveals a globally distributed and multicenter collaboration network involving the major countries and regions contributing to organoid biobanking research (Figure 3B). Overall, the international collaboration network is mainly concentrated in North America, East Asia, and Western Europe, indicating both strong geographical clustering and extensive cross-regional connectivity. In terms of publication output, China ranks first with 499 papers, followed by the United States (n = 303), the Netherlands (n = 131), Germany (n = 126), and the United Kingdom (n = 109). While these findings indicate that publication activity in organoid biobanking remains concentrated in a relatively small group of scientifically leading countries, it should be noted that this distribution may be scale-driven, largely reflecting the overall scientific output and baseline research capacity of each nation rather than a specific thematic prioritization of organoid biobanking research. Beyond the top five, Italy (n = 82), Japan (n = 56), France (n = 54), Spain (n = 47), and Switzerland (n = 40) also show consistently high research output scale, highlighting the continued importance of both continental Europe and East Asia in this field.

The United States serves as the principal network hub, linking major research regions across continents—particularly with the Netherlands and Germany, reflecting sustained transatlantic collaboration. China, while remaining anchored by its partnership with the United States, has also expanded collaborative ties with Asia-Pacific and European partners, signaling the progressive integration of East Asian research into the global organoid community. Collectively, these patterns reveal a core–periphery structure in which geographic proximity and historical scientific alliances shape the topology of international cooperation. The country collaboration network suggests that organoid biobanking research is characterized by a core group of highly productive countries combined with increasingly active cross-regional cooperation, reflecting a globally connected but geographically concentrated global research landscape.

2.2.3. Institutional collaboration network: Core hubs and distribution of contributions

We visualized the collaboration structure among major institutions in organoid biobanking research. After applying a minimum threshold of seven publications, a total of 149 institutions met the inclusion criterion, indicating broad institutional participation in the field (Figure 3C). Among these institutions, University Medical Center Utrecht exhibits the highest total link strength (n = 425), indicating that it is not only highly productive but also the most extensively connected institution in the

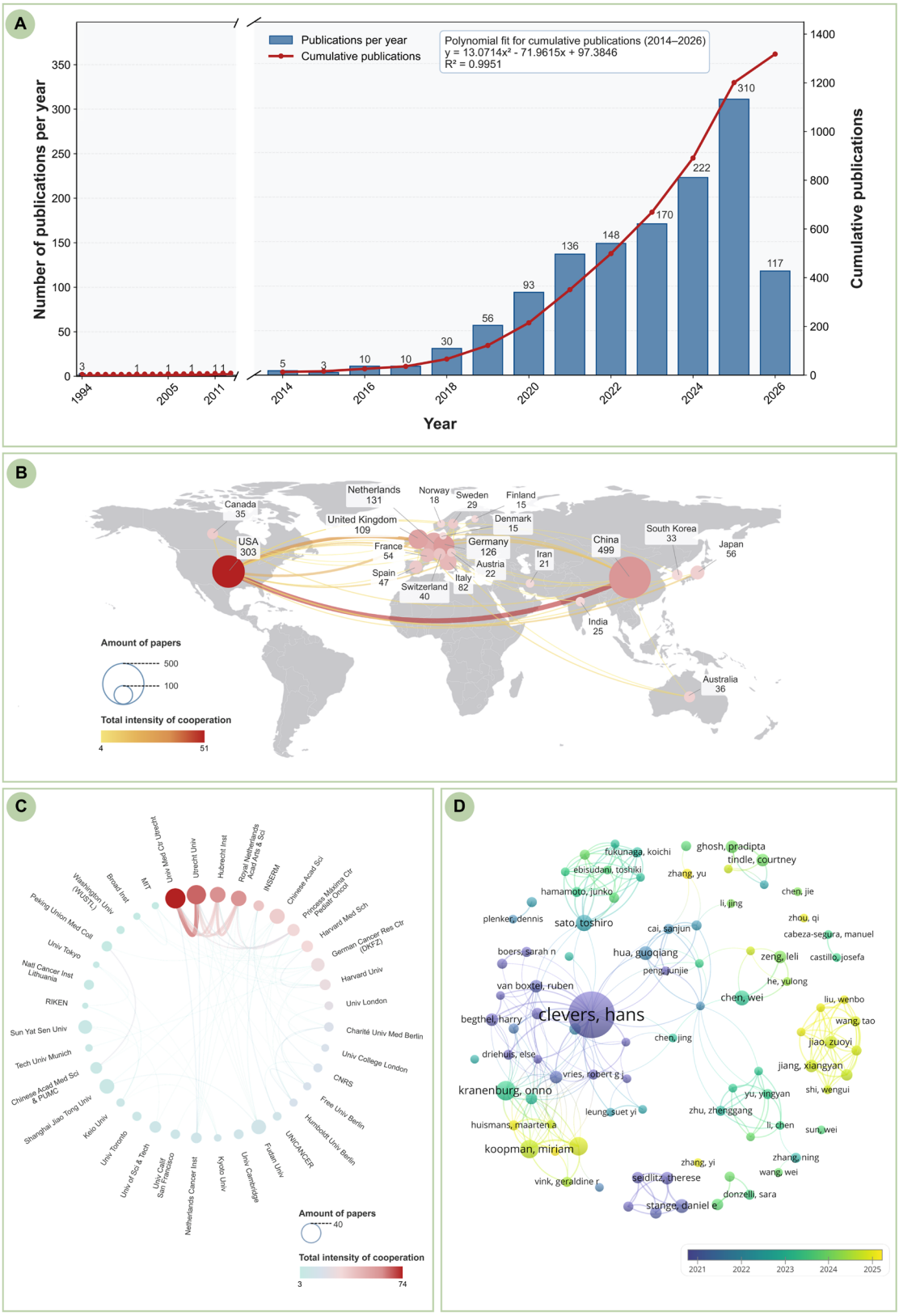

Figure 3. Overview of the research landscape of organoid biobanking: (A) Annual publication trends. (B) Global patterns of international collaboration in organoid biobanking research, (C) institutional contributions to organoid biobanking research, and (D) author co-authorship network.

collaboration network. It is followed by Utrecht University and the Hubrecht Institute, suggesting that the Utrecht-entered research cluster plays a particularly prominent role in organoid biobanking research. At the pairwise level, the strongest institutional collaboration is observed between University Medical Center Utrecht and Utrecht University ($n = 74$), identifying this pair as the most tightly linked cooperative unit in the field. The second strongest collaboration occurs between the Hubrecht Institute and the Royal Netherlands Academy of Arts and Sciences ($n = 49$), further emphasizing the strong internal coherence of the Dutch institutional network in organoid biobanking research.

The top five institutions by publication output—University Medical Center Utrecht ($n = 83$), Utrecht University ($n = 76$), Hubrecht Institute ($n = 50$), Royal Netherlands Academy of Arts and Sciences ($n = 49$), and the Chinese Academy of Sciences ($n = 47$)—illustrate a dual-center structure: European institutions, particularly those in the Netherlands, maintain a dominant position, while the Chinese Academy of Sciences signals the growing contribution of Chinese research organizations. Overall, the institutional network reveals a mature, platform-based collaborative structure characterized by dense cooperation among a limited number of core hubs and gradual expansion toward broader inter-institutional engagement.

Several caveats should be considered when interpreting the collaboration network described above. First, the actual scale of organoid biobanks at different centers may influence the observed collaboration patterns. Larger biobanks, with greater sample diversity and storage capacity, are inherently more likely to engage in multi-center collaborations, potentially inflating their centrality metrics within the network. Future studies could benefit from normalizing collaboration metrics by biobank size (e.g., number of stored organoid lines, annual sample distribution volume) to enable more meaningful cross-center comparisons of collaborative intensity. Second, regulatory restrictions on biomaterial exchange between countries may impose structural barriers to international collaboration that are not captured by bibliometric analysis alone. National and international regulations—including the Nagoya Protocol on access and benefit-sharing of genetic resources, the Food and Drug Administration (FDA) and the European Medicines Agency tissue governance frameworks, and China's Regulations on the Administration of Human Genetic Resources—establish legal requirements for the cross-border transfer of biological samples. These regulatory frameworks may partially explain the observed pattern in which geographically or politically proximate countries exhibit stronger collaboration ties, as shared regulatory environments or bilateral agreements can facilitate biomaterial exchange. Consequently, the collaboration network topology likely reflects not only scientific affinity but also the enabling or constraining effects of the regulatory landscape.

2.2.4. Author collaboration patterns: Central leadership and diversified modalities

Co-authorship network analysis, comprising 4,994 researchers, delineates the distribution and collaborative structure of the organoid biobanking community (Figure 3D). The network is centered on Clevers, Hans, whose node is the largest and most densely connected, indicating a prominent scholarly influence and a central coordinating role in the field. Several tightly linked author subgroups are organized around this core, including collaborations involving Begthel, Harry; Driehuis, Else; and Vries, Robert G. J. In parallel, other relatively distinct collaborative substructures are visible, including groups associated with Sato, Toshiro and Kranenburg, Onno. The temporal overlay further shows that authors located near the network center are generally associated with earlier average publication years, whereas several peripheral contributors are colored closer to recent years, suggesting the continued entry of new researchers alongside stable collaboration among established core teams.

2.2.5. Publication characteristics: Journal distribution and disciplinary convergence

Journal-level analysis showed that organoid biobanking research is primarily disseminated through journals in oncology, cell biology, translational medicine, and general biomedicine, highlighting the highly interdisciplinary nature of the field. In terms of publication output, *Cancers* was the most productive journal, with 34 papers, followed by *Journal of Experimental & Clinical Cancer Research* ($n = 31$), *International Journal of Molecular Sciences* ($n = 27$), *Cancer Research* ($n = 26$), and *Nature Communications* ($n = 24$) (Figure 4A). This distribution reflects the broad expansion of applied research in tumor organoids and translational exploration, yet it does not fully represent the intellectual trajectory and milestone breakthroughs of the field. The technology-defining and field-shaping advances in organoid research have predominantly been published in high-impact multidisciplinary journals including *Nature* and *Cell*, as well as top-tier specialist journals such as *Gut*. These landmark publications—including the first adult stem cell-derived intestinal organoid system[9], the self-organizing optic cup model[10], the cerebral organoid platform[6], and the first large-scale living biobank of colorectal cancer organoids[17]—have shaped the core conceptual and technical framework of the entire field. Studies in journals such as *Cancers* and *Cells* primarily represent expanded applications, incremental validation, and methodology optimization built on these foundational paradigms, rather than the trajectory-setting breakthroughs. Collectively, the

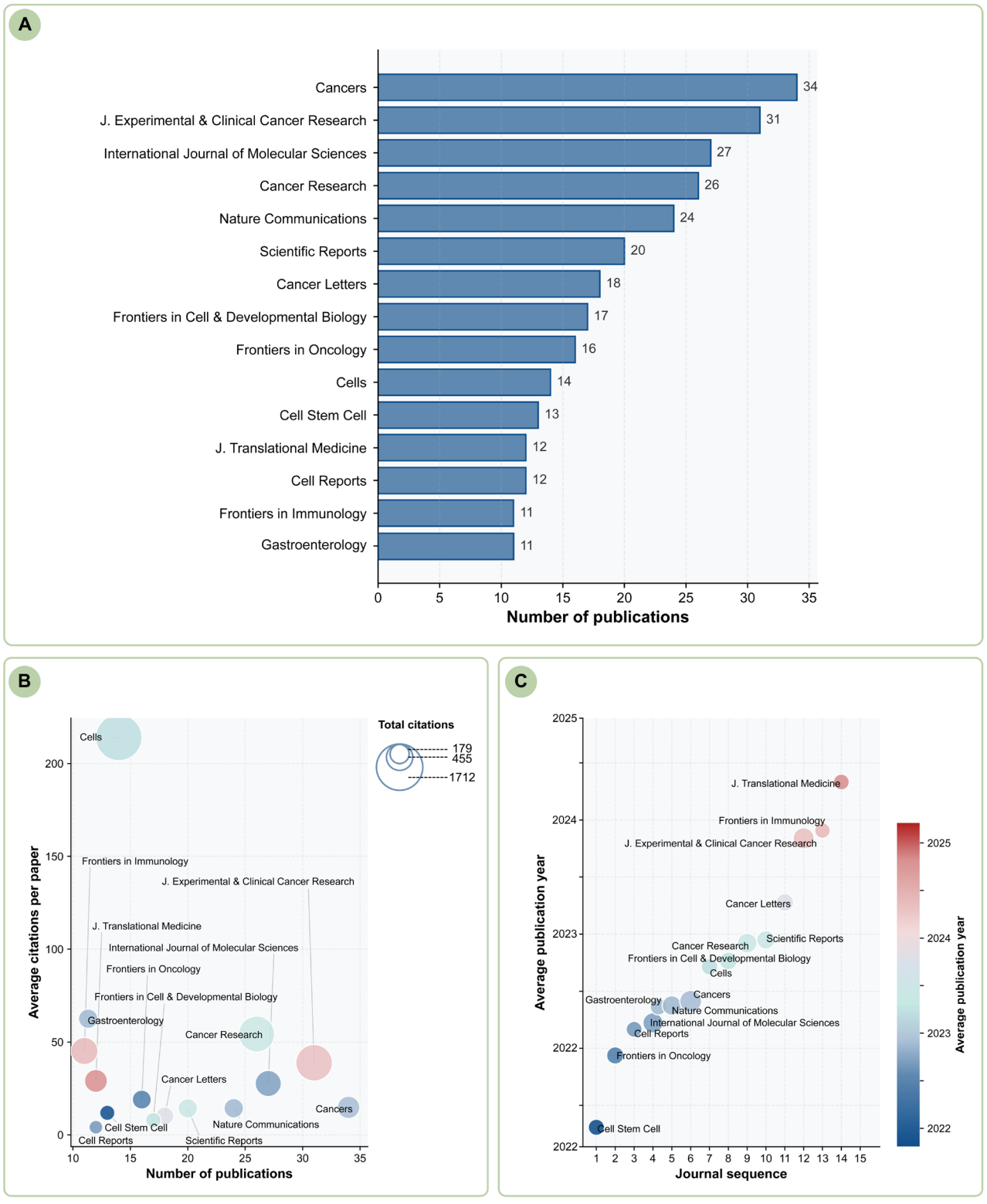

Figure 4. Journal distribution characteristics and interdisciplinary convergence in organoid biobanking research. (A) Distribution of the top 15 journals by number of publications. (B) Strategic positioning bubble plot of journals. (C) Time-overlay plot of journals.

publication landscape suggests a two-tier structure: high-impact general and specialist journals drive conceptual and technological breakthroughs, while specialized oncology and cell biology journals carry the bulk of incremental and applied research, together supporting the rapid growth of the organoid field.

Productivity and citation impact, however, are not fully aligned (Figure 4B). Although *Cancers* and *Journal of Experimental & Clinical Cancer Research* dominate by volume, *Cells* exhibits disproportionately high average citation impact, while *Cancer Research* and *Frontiers in Immunology* demonstrate high citation impact despite lower output. This stratified ecology suggests that knowledge dissemination in the field is driven not solely by the most prolific journals but also by venues with strong disciplinary visibility or rapid dissemination capacity.

The time-overlay analysis further revealed an evolution in journal preferences over time (Figure 4C). Earlier contributions were more strongly associated with journals such as *Cell Stem Cell*, *Frontiers in Oncology*, *Cell Reports*, and *Nature Communications*, suggesting that the field initially developed at the interface of stem cell biology, oncology, and broadly scoped high-impact biomedical journals. By contrast, peer-reviewed journals such as the *Journal of Translational Medicine*, *Frontiers in Immunology*, *Journal of Experimental & Clinical Cancer Research*, and *Gastroenterology* showed more recent average publication years, indicating that current research activity is increasingly oriented toward translational medicine, immune-related studies, clinically focused oncology, and gastrointestinal disease applications. Taken together, the combined evidence from publication output, citation performance, and temporal overlay supports the view that organoid research is now sustained by a multi-dimensional peer-reviewed journal structure spanning oncology, cell and developmental biology, molecular medicine, immunology, gastroenterology, and translational research, reflecting the progressive convergence of basic and clinically oriented research agendas.

2.3. Evolution of research hotspots

2.3.1. Temporal migration of hotspot keywords: From stem cell foundations to oncology and precision-oriented applications

The keyword timeline bubble plot revealed a clear temporal shift in organoid biobanking research during the period from 2018 to 2025 (Figure 5A). Early activity was anchored mainly in stem cell biology and foundational culture systems, whereas later work increasingly converged on oncology, precision medicine, and therapeutic application. During the earlier phase, "Stem cells," "pluripotent stem cells," and "induced pluripotent stem cells" remained recurrent high-frequency terms, indicating that the field initially developed around questions of cell source, differentiation potential, and culture optimization. At the same time, the continued presence of terms such as "3D culture" and "patient-derived organoids" underscores the enduring importance of model establishment and *in vitro* tissue reconstruction.

After 2021, disease- and cancer-related keywords increased markedly in frequency. This trend became especially prominent in 2024–2025, when "cancer," "colorectal cancer," "tumor microenvironment," "drug screening," and "personalized therapy" rose in parallel. In 2025, "cancer" reached 45 occurrences, followed by "personalized therapy" (n = 42), "stem cells" (n = 39), "tumor microenvironment" (n = 27), and "colorectal cancer" (n = 26). These changes indicate a shift in emphasis from foundational system development toward functional and clinically relevant applications. The concurrent increase of terms such as "immunotherapy," "liver cancer," "pancreatic cancer," and "breast cancer" further suggests growing specialization of organoid research across tumor contexts and therapeutic approaches.

2.3.2. Thematic consolidation around disease applications: Oncology dominates while platform technologies continue to advance

The theme river plot further clarified the broader reorganization of research priorities (Figure 5B). Among the six thematic domains, "disease and oncology" remained the dominant component throughout the study period and showed the most pronounced expansion between 2023 and 2025, emerging as the primary contributor to the overall increase in thematic intensity. This pattern closely mirrors the parallel rise of cancer-associated keywords in panel a and indicates that disease-oriented, especially oncology-centered, applications now shape the major trajectory of the field.

At the same time, "stem cells and differentiation" remained consistently active, indicating that stem-cell source and differentiation control continue to provide the conceptual and technical foundation of organoid research. "Drug screening and precision" expanded substantially after 2021 and reached a high level in 2024–2025, suggesting increasing use of organoid platforms for functional drug evaluation and individualized therapeutic decision-making. By comparison, "microphysiological platforms" and "bioengineering and materials" remained smaller in scale but showed sustained growth in the later years, reflecting the increasing importance of microfluidics, matrix design, and bioengineering-based reconstruction in expanding organoid applications. The universal decline in 2026 likely stems from incomplete annual indexing rather than an actual drop in research activity.

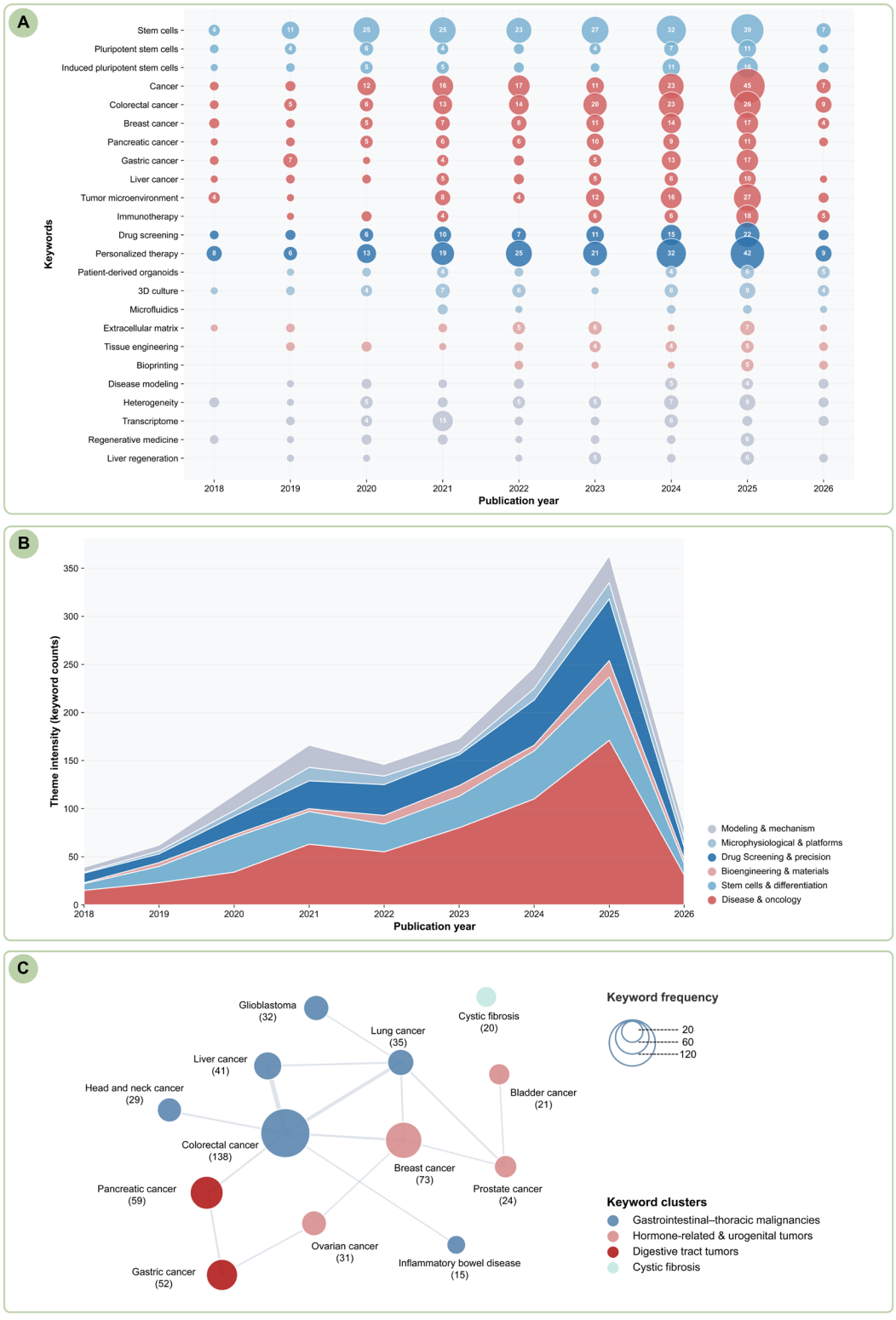

Figure 5. Keyword evolution, thematic consolidation, and disease-model structure in organoid research. (A) Keyword timeline bubble plot. (B) Theme river plot. Filtered keywords were aggregated into six thematic domains, and the vertical area of each stream represents the relative annual intensity of that theme, illustrating changes in thematic emphasis over time. (C) Disease-related keyword clustering network. Nodes represent disease-associated keywords, node size indicates keyword frequency, links indicate co-occurrence relationships, and colors denote cluster membership, thereby showing the structured organization of disease applications in organoid research.

2.3.3. High-burst keywords and associated-disease profiling

The disease-related keyword clustering network revealed a clearly structured application landscape in which oncology dominates as the primary disease context. Within this network, "colorectal cancer" formed the largest and most central node, with a frequency of 138, and maintained extensive connections with multiple other disease terms (Figure 5C). This position indicates that colorectal cancer is not only the most intensively studied disease model, but also a major bridging topic linking otherwise distinct disease domains. Closely connected terms included "liver cancer" (n = 41), "lung cancer" (n = 35), "glioblastoma" (n = 32), and "head and neck cancer" (n = 29), together constituting the principal cluster centered on gastrointestinal and other solid tumors.

Two additional tumor-oriented clusters were also evident. One was centered on "breast cancer" (n = 73) and grouped with "ovarian cancer" (n = 31), "prostate cancer" (n = 24), and "bladder cancer" (n = 21), forming a hormone-related and genitourinary tumor cluster. The second consisted primarily of "pancreatic cancer" (n = 59) and "gastric cancer" (n = 52), representing a more compact digestive-tract tumor module. By contrast, "cystic fibrosis" (n = 20) appeared as a relatively isolated node, suggesting that non-oncological disease applications have entered the field but remain peripheral compared with the dominant cancer-oriented research landscape. Taken together, these patterns indicate that organoid disease modeling has evolved into a colorectal cancer-centered multi-tumor network with limited but discernible expansion into non-neoplastic disease settings.

3. Organoid biobanks: From model innovation to a resource ecosystem

Biobanks represent an indispensable interface connecting fundamental research and clinical translation, as the intrinsic quality of biological resources directly determines the reliability of experimental results and the efficiency of translational applications.[22] Beyond clinical biospecimens, traditional preclinical studies have largely depended on 2D cell lines and patient-derived xenograft (PDX) models.[40] Alongside these platforms, bioengineered 3D models and organ-on-a-chip systems have undergone continuous technical refinement, together forming a continuous evolutionary continuum of preclinical modeling tools (Figure 6A). Conventional 2D monolayer cultures cannot replicate the complex 3D microenvironment present in native tissues, leading to considerable discrepancies in intercellular communication, extracellular matrix (ECM) interactions, and metabolic pathway activity relative to native physiological conditions.[41]

Although PDX models maintain the heterogeneity of primary tumors, their application is severely restricted by inherent interspecies differences in immunodeficient mice—such as the lack of functional human hepatic CYP3A4 activity, long preparation cycles of 4–8 weeks, and high costs often exceeding USD 15,000 per model.[40] These combined limitations render PDX systems challenging for large-scale biobank development.[22] Bioengineered models utilizing 3D printing and hydrogel scaffolds can partially reconstruct tumor microarchitecture and tissue-level structure to support more physiologically relevant cell coculture, yet they remain hindered by low standardization, poor batch-to-batch consistency, and an inability to fully replicate the complexity of the *in vivo* microenvironment.[42] Organ-on-a-chip systems use microfluidics to mimic organ anatomy, fluid shear stress, and physiological niches, allowing precise regulation of culture parameters and supporting organ-level functional analysis and multi-organ integration. Nevertheless, these systems require advanced technical expertise and high costs, and the functional maturity of *in vitro* models remains lower than that of native organs.[43,44]

Driven by advances in 3D cell culture systems, organoids have emerged as a transformative modeling platform that reconstructs native organ structure and function through intrinsic self-organization programs.[41] PDOs stably maintain patient-specific disease-related genomic characteristics, including key oncogenic mutations and pathogenic variants associated with hereditary disorders, establishing PDOs as a foundational resource for next-generation organoid biobanking.[22] The 2023 FDA Modernization Act, which encourages the adoption of alternative approaches to animal experimentation, has further underscored the strategic value of organoid biobanks in predictive toxicology assessment and prediction of clinical therapeutic responses. Together, these technical and policy advances are reshaping the foundational framework of biomedical research, facilitating a gradual transition from animal-dependent systems to human-relevant *in vitro* modeling platforms.

Quality control for organoid biobanks requires full-process integration spanning cellular source authentication, culture system establishment, microenvironmental regulation, and long-term storage management. During biospecimen collection, donor ethical eligibility, pathological diagnosis, and genetic background require strict validation.[41] For tumor organoids, the anatomic location, histological subtype, and somatic mutation spectrum of primary lesions must be precisely documented; for genetic disease models, complete pedigree information is indispensable.[22] Standardized medium preparation and real-time monitoring systems should be adopted during organoid culture establishment, and live-cell imaging can

be applied to dynamically evaluate organoid morphology and differentiation state, thereby stabilizing inter-batch reproducibility.[45] Microenvironmental regulation needs to mimic *in vivo* physiological conditions: immune cell coculture systems may be incorporated in tumor organoid models, while neural organoids frequently demand optimized ECM components to support axonogenesis.[22] For storage management, intelligent liquid nitrogen storage systems integrated with Internet-of-Things–based telemetry are recommended to enable real-time tracking of temperature, sample location tracking, and access records, with customized cryopreservation protocols designed for specific research purposes. Technical parameters at each step should be adjusted according to the biobank's positioning, such as oncologic or hereditary disease modeling.[22] The construction of a multi-level and multi-dimensional quality control system is crucial to maintain biological fidelity and ensure experimental reproducibility of organoid resources.

3.1. Selection of cellular sources: A versatile foundation for diverse research objectives

Organoid construction typically relies on four primary categories of cellular sources: embryonic stem cells (ESCs), adult stem cells (ASCs), tissue-derived cell pools (TDCPs), and iPSCs (Figure 6B).[46] Among these, ESCs and iPSCs play a central role, supporting a wide range of experimental and translational applications. ESCs are isolated from the inner cell mass of blastocyst-stage embryos and possess stable pluripotent characteristics. Under defined induction conditions, these cells can commit to lineages representative of all three embryonic germ layers, including endoderm, mesoderm, and ectoderm, ultimately giving rise to functional cell types and tissue structures of multiple organs including the brain, kidneys, liver, lungs, and intestine.[47] These properties enable ESC-based systems to faithfully model early embryogenesis and organogenesis and are therefore indispensable tools in developmental biology.[48] iPSCs are generated by the ectopic expression of defined transcription factors including octamer-binding transcription factor 4, SRY-box transcription factor 2, Krüppel-like factor 4, and cellular myelocytomasis oncogene, which reprogram somatic cells to a pluripotent state comparable to embryonic stem cells.[47] Beyond their extensive multilineage differentiation potential, iPSCs hold a unique advantage in being directly derivable from individual patients. This feature effectively addresses the ethical constraints associated with ESCs and lowers the likelihood of immune rejection in autologous transplantation settings.[49] For disease modeling, iPSCs show particular strength in retaining the unique genomic background of individual donors, supporting the establishment of high-fidelity *in vitro* systems for complex diseases including neurodegenerative conditions and liver diseases.[50] These models recapitulate disease initiation and progression, facilitate mechanistic dissection, and support the identification and preclinical evaluation of candidate therapeutics.[51] iPSC-based systems therefore serve as essential platforms for the study of genetic diseases, supporting in-depth exploration of molecular pathological mechanisms, the design of individualized therapeutic regimens, and progress in regenerative medicine research.[52]

Unlike pluripotent stem cells including ESCs and iPSCs, ASCs are isolated from adult tissues, exhibit tissue specificity, and possess only tissue-specific differentiation competence.[53] The primary strength of ASCs lies in their rapid commitment to defined cell lineages, allowing efficient reconstruction of target tissue architectures with markedly shortened culture cycles.[54] TDCPs, by contrast, comprise multiple cell types whose composition and proportions more closely reflect those of the native tissue.[55] These pools frequently contain diverse differentiated cell types, thereby conferring clear advantages in recapitulating the tissue microenvironment and enhancing the physiological fidelity of organoid models.[56] The intrinsic cellular diversity and complexity of TDCPs enable a more accurate replication of native tissue physiology, offering a compelling route for organoid construction.

In summary, ESCs and iPSCs rely on their pluripotent potential to support multilineage differentiation and the generation of organoids with structural complexity. ASCs and TDCPs, by leveraging tissue specificity and cellular heterogeneity, rapidly construct defined tissue architectures while preserving high microenvironmental fidelity. These four cellular sources collectively form a flexible and complementary toolkit that can be adapted to meet diverse experimental demands in organoid-related biological research.[46]

3.2. Construction of 3D culture systems: Core support for a biomimetic microenvironment

The essence of organoid technology lies in recapitulating the coupled complexity of macro- and micro-environmental cues *in vivo* using *in vitro* miniaturized models. The 3D culture system is the structural backbone that underpins both fidelity and reproducibility.[57] Over the past decade, progressive breakthroughs integrating stem cell biology, biomaterial engineering, and micro/nanofabrication technologies have redefined conventional 3D culture systems. No longer merely an alternative to 2D monolayer cultures, these platforms have evolved into highly controllable biomimetic systems with programmable spatiotemporal regulation, multiscale structural assembly, multicellular crosstalk, and multiphysical signal simulation.[58] Guided by the developmental course, mechanical features, metabolic patterns, and the immune microenvironment of the target organ, researchers can flexibly integrate a suite of technical modules, including hydrogel-based ECM analogs, air–

liquid interfaces (ALIs), microfluidic devices, bioreactors, microwell arrays, and suspension culture systems. Such modular combinations enable organoid models to evolve from mere morphological mimicry toward the faithful recapitulation of *in vivo* physiological and pathological mechanisms (Figure 6C).

For matrix hydrogel culture, apart from the batch variability of animal-derived Matrigel, undefined bioactive ingredients hinder clinical translation, while animal-origin raw materials also raise ethical restrictions. For ALI culture, rigid polarity requirements for culture substrates restrict its application scope, and the system cannot be easily combined with vascularized construction modules to simulate complete organ structures. Microfluidic culture suffers from expensive hardware and complicated operating workflows, making large-scale routine screening challenging. Bioreactors carry risks of excessive shear stress that can damage organoid integrity and require laborious repeated parameter tuning to balance nutrient delivery and tissue viability. Scaffold-free suspension culture fails to provide stable extracellular niche cues, leading to uncontrolled morphological differentiation of organoids for certain tissue lineages. Microwell array platforms rely on high-cost microfabrication and static structures and are incapable of simulating dynamic mechanical stimuli such as intestinal peristalsis.

Table 1 presents the six representative culture strategies.

3.2.1. Matrix hydrogel approach

The hydrogel-based matrix approach continues to represent the most widely adopted gold standard for 3D organoid culture, offering an injectable and cross-linkable ECM substitute that sustains cell viability within a permissive 3D microenvironment. Matrigel, enriched in laminin-111, collagen IV, heparan sulfate proteoglycans, and more than 700 bioactive growth factors, undergoes a thermally triggered sol-gel transition between 10°C and 37 °C. This material effectively recapitulates hallmark features of the tumor microenvironment, including soft matrix stiffness (Young's modulus E ≈ 0.5 kPa) and nanoporous architecture (50–200 nm), and is therefore extensively used for endoderm-derived organoids such as intestine, liver, and pancreas.[59] Nonetheless, clinical translation of Matrigel-based systems is hindered by batch-to-batch inconsistency, ethical considerations linked to animal-derived components, and the presence of uncharacterized constituents.[57]

Table 1. Comparison of six three-dimensional organoid culture systems

Culture method	Suitable organs	Advantages	Limitations	References
Matrix hydrogel approach	Intestine, liver, pancreas, gastrointestinal tract, most solid tumor organoids	Gold standard; high biomimicry; supports self-organization; widely used and validated	Batch variability; animal-derived matrix ethical concerns; undefined components; poor clinical translation compatibility	57,59
Air–liquid interface	Lung, skin, cornea, endometrium, airway epithelia	Promotes epithelial maturation and polarity; enhances oxygenation; ideal for mucosal and respiratory models	Strict substrate polarity requirements; difficult to integrate with vascular systems; limited to epithelial tissues	60–63
Microfluidic culture	Intestine, liver, kidney, neuron, multi-organ systems	Precise spatiotemporal control; enables drug gradient and shear stress modulation; supports ADME-Tox and multi-organ coupling	High technical barrier; complex operation; costly equipment; low scalability for routine labs	64,65
Bioreactors	Liver, retina, islets, large-scale organoids	Overcomes diffusion limits; supports large organoid growth; improves metabolic maturity; high industrial throughput	Large equipment footprint; high shear stress risk; complex parameter optimization	66–68
Suspension formats	Mammary gland, tumor organoids, scalable expansion	Scaffold-free; high expansion efficiency; uniform size; low central necrosis; high-throughput compatible	Lacks structural niche; limited control over morphology; not suitable for some tissue types	58,67,69
Microwell arrays	Intestine, high-throughput screening models	Ultra-uniform organoid size; structure–function mapping; integrated TEER detection; compatible with single-cell analysis	High fabrication cost; fixed structure; difficult to recapitulate dynamic mechanical forces	70–72

Abbreviations: ADME: Absorption–distribution–metabolism–excretion; TEER: Transepithelial/transendothelial electrical resistance.

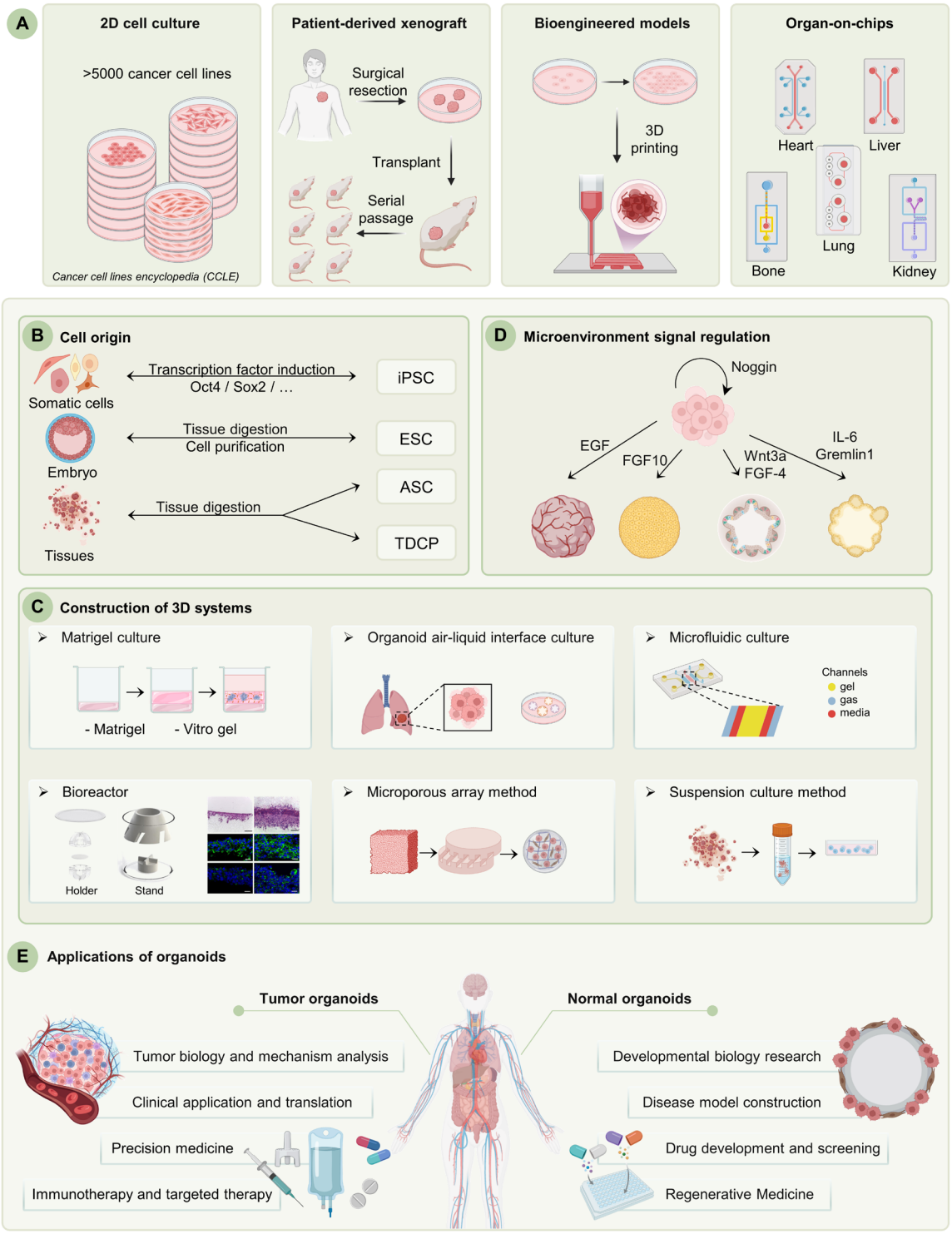

Figure 6. Cultivation and application of organoids. (A) Four currently common methods for disease model construction, including 2D cell culture, patient-derived xenografts, 3D printing, and organ-on-a-chip. (B–D) Methods for organoid cultivation, including (B) cell origin, (C) 3D system construction, and (D) microenvironment regulation. (E) Application directions of tumor organoids and normal organoids. Created in BioRender. Liu, J. (2026) https://BioRender.com/alqwckv.

Abbreviations: ASC: Adult stem cell; CCLE: Cancer Cell Lines Encyclopedia; EGF: Epidermal growth factor; ESC: Embryonic stem cell; FGF-4: Fibroblast growth factor 4; FGF10: Fibroblast growth factor 10; iPSC: Induced pluripotent stem cell; IL-6: Interleukin-6; TDCP: Tissue-derived cell population; Wnt3a: Wingless-type MMTV integration site family, member 3a.

Next-generation animal-free hydrogels, including VitroGel, permit independent modulation of ligand density (e.g., arginine–glycine–aspartate at 0.5–3 mM), degradability (matrix metalloproteinase-sensitive motifs), and stiffness[73], while supporting cell encapsulation at room temperature. Such platforms facilitate organoid formation from primary tumor specimens within 24 h and are compatible with subsequent co-transplantation into patient-derived xenograft models.[74] Recent work has further combined Matrigel/VitroGel with microfluidic platforms to establish a dual-mode gel-perfusion culture regimen. In this system, gel-based anchorage supports initial morphogenetic development, after which enzymatic dissociation allows organoids to be transferred into perfused pathways for improved metabolic maturation. The proportion of central necrosis can be reduced to less than 5%. Looking forward, synthetic biology-driven modular ECM systems, in which recombinant proteins secreted by cells undergo in situ cross-linking, may eliminate reliance on exogenous gels and enable cell-autonomous niche construction.[58]

3.2.2. Air–liquid interface

The ALI paradigm recapitulates the native "breathing" interface of epithelia—an apical surface exposed to air and a basolateral surface immersed in medium.[58] Supported by Transwell membranes, cells establish polarity across 0.33 μm pores, while surface tension forms an ultrathin apical liquid film (<5 μm). The resultant oxygen partial pressure (≈120 mmHg) closely approximates that of the airway gradients *in vivo*. Under these conditions, alveolar organoids spontaneously form 100–200 μm cystic structures, with an eight-fold increase in the secretion of surfactant protein B compared with submerged culture.[61] When combined with genome-wide Clustered Regularly Interspaced Short Palindromic Repeats screening, ALI systems have successfully modeled the depletion trajectory of type II alveolar cells following SARS-CoV-2 infection.[62] Recent advances integrate ALI with stretchable membranes to emulate breathing at 0.2 Hz and 5% linear strain, inducing a trans-epithelial pressure differential of ≈0.3 cm H_2O and markedly enhancing the differentiation of Club cells into ciliated cells.[63] The applicability of ALI culture has expanded beyond the respiratory tract to include stratified epithelial tissues, including the epidermis, cornea, and endometrium, all of which depend on air exposure to drive keratinization or glycocalyx maturation.[60] However, ALI imposes stringent constraints on substrate polarity and remains challenging to integrate with vascular circuits; future iterations will likely leverage membrane–microvasculature composite chips to assemble physiologically coupled "airway-vascular" units.

3.2.3. Microfluidic culture

Microfluidic techniques have brought organoid culture into an era of spatiotemporal encoding.[64] Using Braille valves, piezoelectric micropumps, and electrochemical sensor arrays, fL-nL droplets can be generated at 10^2–10^3 μm length scales, enabling the simultaneous control of linear drug gradients (0–10 μM; $R^2 > 0.99$) and shear stress (0.1–20 dyn cm^{-2}). A representative multi-organ chip developed by Harvard researchers connects intestinal, liver, kidney, and neuronal organoids through three sequential microchannels with independently regulated flow rates, which accurately recapitulates the oral first-pass pharmacokinetic behavior, with Cmax values differing by less than 9% from clinically observed human data.[58] Advanced closed-loop microfluidics integrates online solid-phase extraction–liquid chromatography–mass spectrometry to deliver end-to-end ADME-Tox profiling within 30 minutes—approximately 100-fold faster than standard 96-well plate assays.[58] Notably, the advent of 3D-printed hydrogel microvalves enables hybrid "chip-gel" systems wherein hydrogel regions provide authentic 3D microenvironments, whereas valve regions orchestrate dynamic perfusion, effectively decoupling matrix composition from fluid mechanics. This configuration supports adjustable spatiotemporal conditions for drug-immune cell interactions in tumor-immune co-culture models. As AI-mediated feedback continues to mature, microfluidic organoid systems are expected to develop into digital twin platforms that support real-time optimization of personalized therapeutic strategies.

3.2.4. Bioreactors and suspension culture

In static culture systems, oxygen and nutrient diffusion are typically limited to approximately 200 μm, often resulting in morphologically intact yet metabolically impaired organoids.[58] By establishing combined convective-diffusive transport fields, bioreactor systems effectively extend the viable diameter of organoids to 1–2 mm.[67] Stirred bioreactors operating at 30–80 rpm generate Kolmogorov-scale microvortices (λ ≈ 50 μm), maintaining shear stresses of <5 dyn cm^{-2} while elevating albumin secretion from hepatic organoids by roughly 4.5-fold.[67] Rotating wall vessel systems, with horizontal rotation at 10–30 rpm, simulate microgravity, reducing apoptosis to approximately 2%. In these systems, retinal organoids acquire functional electrophysiological activity within four weeks, roughly 30% more rapidly than in static cultures.[75] The latest "microfluidic bioreactors" couple silicon-based microhole arrays to external peristaltic pumps, enabling independent perfusion per well (0.1–1 μL min^{-1}) and synchronous culture of approximately 1,000 hepatic organoids with a coefficient of variation of <5%, providing industrial-grade throughput for toxicology screening.[68] Cutting-edge sensor-integrated bioreactors further incorporate real-time monitoring of oxygen, pH, and lactate levels, paired with machine-learning algorithms to dynamically

adjust agitation and perfusion for sustained metabolic stability. Under such optimized conditions, iPSC-derived islet organoids reach approximately 80% of the *in vivo* glucose-stimulated insulin secretion level by day 28.[66] A key future direction lies in multi-organ coupling—linking liver, kidney, and cardiac organoids within fluidic circuits to emulate drug–organ interaction networks and establish human-relevant platforms for systemic toxicology evaluation.[76]

In parallel, suspension formats eliminate exogenous matrices, enabling "scaffold-unbiased" scale-up. Spinner flasks at approximately 50 rpm deliver energy dissipation of roughly 0.3 W m^{-3}, achieving a 50-fold expansion of mammary organoids within seven days while preserving ER^+ subpopulations above 60%.[58] Addition of Rho-associated coiled-coil kinase inhibitors combined with epidermal growth factor (EGF) and fibroblast growth factor (FGF)-2 stimulation stabilizes spheroid diameters at 150 ± 20 μm and restricts central necrosis to below 5%.[69] Microfluidic suspension chips employing "vortex cushions" reduce shear to approximately 0.05 dyn cm^{-2}, permitting synchronous culture of nearly 10,000 tumor organoids. Drug IC_{50} values (half-maximal inhibitory concentration) show strong correlation with *in vivo* PDX therapeutic responses (R^2 = 0.85).[58] Acoustic levitation at 2 MHz affords contactless rotation, eliminating wall effects. Neural organoids cultured under these conditions develop laminar layering, with electrophysiological burst frequencies closely matching gestational-age trajectories (r = 0.92).[67] A promising direction is immune–tumor co-suspension: CD3/CD28-functionalized microbeads can assemble "co-spheroids" of T cells and tumor organoids, supporting real-time cytotoxicity readouts for immunotherapy.[77]

3.2.5. Microwell arrays

Microwell arrays provide direct structure-function mapping, compressing the coefficient of variation of organoid size distribution to below 3%.[72] Silicon arrays fabricated via deep reactive ion etching achieve aspect ratios up to 20:1, with platinum microelectrodes integrated at the well bottoms for simultaneous measurement of transepithelial electrical resistance across 1,024 intestinal organoids, thereby coupling morphological metrics with barrier function. Polydimethylsiloxane–hydrogel composite microwells introduce collapsible sidewalls that constrict aperture by approximately 30% under 5 kPa negative pressure, mimicking intestinal peristalsis and inducing villus-like folds. The resulting villus-to-crypt ratio approaches 3:1, approximating the adult intestine.[70–72] Recent work couples microwell arrays to laser microdissection for non-destructive harvesting of single cells and organoids.[78] Subsequent single-cell RNA sequencing has identified five metastable cellular states of $LGR5^+$ stem cells distributed along the crypt-villus axis. Moving forward, "kilowell–kiloomics" strategies could establish large-scale phenotype-genotype atlases of organoids, underpinning AI-driven precision medicine.[79]

3.3. Microenvironmental signal regulation: Molecular mechanisms sustaining functional homeostasis

The regulation of microenvironmental signals is pivotal for successful organoid construction and the sustained preservation of function. Organoid methodologies have advanced rapidly from basic research tools to translational platforms central to tissue engineering and regenerative medicine.[80] Microenvironmental control in organoid culture orchestrates a network of cues that emulate *in vivo* signaling complexity, thereby precisely modulating cellular proliferation, lineage commitment, and tissue morphogenesis (Figure 6D). Two principal regulatory axes govern organoid culture: stemness preservation and proliferation. Noggin, a selective bone morphogenetic protein (BMP) antagonist, sustains stemness by neutralizing BMP ligands and is indispensable for long-term culture across brain, prostate, pancreatic, lung, gastric, hepatic, and intestinal organoid systems. EGF activates the EGFR–Ras–Raf–MEK–ERK cascade to stimulate epithelial proliferation and support differentiation, ensuring consistent growth across virtually all normal and tumor organoid platforms. These two axes—anti-differentiation and pro-proliferation—form the core signaling backbone that underpins organoid viability and expansion.

Beyond these core signals, organ-specific requirements demand additional fine-tuning. FGF10 modulates both BMP and Wnt pathways, stabilizing structural and functional maturity particularly in gastric and tumor organoids.[81] Wnt3a, acting cooperatively with R-spondin 1, sustains $LGR5^+$ stem cell self-renewal—most critically in intestinal organoids—while tumor-specific supplements (including interleukin [IL]-6 signaling via gp130/signal transducer and activator of transcription 3 and gremlin 1 as a BMP antagonist) more closely recapitulate the native tumor microenvironment to improve preclinical drug-screening accuracy.[82] FGF4 similarly reinforces stem cell self-renewal and suppresses aberrant off-lineage differentiation in intestinal models.[81] Collectively, these supplementary factors exemplify how rational signal combinations, tailored to disease context, transform generic culture media into precision-engineered niche formulations.

Concomitant advances in genetic engineering and real-time imaging have enabled more precise regulation of the organoid microenvironment. For instance, based on Clustered Regularly Interspaced Short Palindromic Repeats/Cas9 technology, the LGR5–mNeonGreen

fluorescent reporter system for human small intestinal stem cells established by Yang *et al.*[83] at Tongji University that enables precise tracking of stem cell dynamics within organoids. Coupled with small-molecule screening, this approach yielded a next-generation human small intestinal organoid platform and recapitulated the dynamic regulation of cell fate via microenvironmental signals. In parallel, microfluidic technologies have revolutionized *in vitro* morphogenetics by precisely governing flow fields and signaling gradients to emulate *in vivo* complexity.[84] Microchannel architectures that establish Wnt gradients, for instance, mimic embryonic morphogen distributions and allow organoids to recapitulate the crypt-villus polarity axis *ex vivo*.[84] Such strategies—integrating biophysical patterning with biochemical signaling—provide innovative models for decoding organogenesis and crucial support for organoid morphogenesis and functional maturation.[66]

The translational potential of microenvironmental signal regulation spans multiple biomedical fields. In disease modeling, the engineering of co-culture systems that precisely control cancer-associated fibroblast–derived cytokines including transforming growth factor-β and IL-6 allows organoid models to recapitulate tumor heterogeneity and stromal-tumor crosstalk, providing an ideal platform for investigating microenvironment-driven drug resistance.[82] In drug development, microenvironment-optimized organoids enable precise expression of drug-metabolizing enzyme systems and improve response prediction accuracy by approximately three- to five-fold higher than that observed in traditional 2D models. In regenerative medicine, hydrogel scaffolds programmed for the temporally staged release of factors such as vascular endothelial growth factor and platelet-derived growth factor BB can guide vascularized organoid differentiation, generating functional biomaterials suitable for transplantation.[66] Notably, the integration of single-cell transcriptomics and spatial multi-omics has enabled systematic mapping of microenvironmental signaling networks, driving organoid technology toward higher-order biomimicry and more authentic physiological reconstruction.

3.4. Classification-oriented biobanking frameworks: Strategies for resource-efficient organization and utilization

As organoid technologies evolve from microenvironmentally controlled culture systems to scalable translational platforms, the establishment of rational, classification-oriented biobanking frameworks becomes essential for maximizing resource efficiency, reproducibility, and clinical relevance. Organoid biobanks, as foundational infrastructures for precision medicine and systems biology, can be systematically organized according to disease category, tissue origin, sample source, pathological subtypes, application fields, and modes of technological integration and storage.[22]

Disease-oriented classification categorizes biobanks into three broad domains: tumor models (encompassing solid, hematological, and rare malignancies), genetic disease models (typically iPSC-derived, targeting conditions such as cystic fibrosis and Duchenne muscular dystrophy), and infectious disease models (e.g., norovirus- or SARS-CoV-2–infected organoids). Within the tumor domain, solid-tumor organoids from lung, gastric, colorectal, breast, and ovarian tumors preserve intratumoral heterogeneity and patient-specific drug response profiles, serving as indispensable platforms for personalized therapeutic screening.[85] Hematological malignancy models require specialized bone-marrow niche culture systems to recapitulate the complex signaling milieu essential for disease pathogenesis investigation.[22] Rare tumor organoids—including pseudomyxoma peritonei and small-cell neuroendocrine carcinoma—fill critical gaps in preclinical modeling where conventional cell lines are unavailable.[22]

Tissue-of-origin classification further refines biobank organization. Patient-derived tumor tissues yield organoids that retain both genetic and phenotypic heterogeneity for tumor evolution and precision oncology studies, while normal tissues from non-diseased regions generate reference organoids for drug screening, toxicity assessment, and regenerative medicine.[22] Healthy-donor tissues provide baseline physiological models and essential disease-model controls. Stem-cell-derived organoids—whether from pluripotent (ESC/iPSC) or adult sources—represent a central biobanking pillar, supporting organogenesis studies, developmental disorder research, and pharmacological screening across neural, cardiac, hepatic, and intestinal systems.[86,87]

Stratification by sample source and pathological subtypes highlights the exceptional translational value of PDOs. Gastric and breast cancer organoids achieve establishment rates exceeding 80%, faithfully preserving tumor architecture, genomic features, and patient-specific chemotherapeutic responses.[85] For example, organoids from 57 of 73 gastric cancer specimens (78% establishment rate) maintained histopathological features and displayed heterogeneous drug sensitivity profiles[85], with transcriptomic analyses revealing upregulation of tumor suppressor genes in chemosensitive organoids versus enrichment of proliferation-associated programs in chemoresistant ones—underscoring their utility as predictive tools for individualized chemotherapy selection.

By contrast, organoids derived from cervical exfoliated cells offer a minimally invasive alternative for generating normal or premalignant models, rendering

them particularly suitable for cancer screening and early-stage mechanistic studies.[22] Such organoids enable early detection of oncogenic risk and support timely diagnostic and therapeutic interventions. Moreover, cervical cancer organoids can be further stratified by pathological subtype—such as squamous cell carcinoma, adenocarcinoma, and clear cell carcinoma—each exhibiting distinct culture requirements and establishment efficiencies.[22] Subtype-specific classification thus facilitates the optimization of culture conditions and improves both organoid generation efficiency and fidelity.

From an application-oriented perspective, organoids demonstrate broad utility across drug development, regenerative medicine, and fundamental biological research. In drug discovery and toxicity testing, colorectal cancer organoids exhibit clinical concordance rates exceeding 80% in chemosensitivity assays, positioning them as reliable platforms for therapeutic screening. Hepatic organoids offer distinct advantages in predicting metabolic toxicity by recapitulating key drug biotransformation pathways. Meanwhile, cardiac organoids allow for the assessment of drug-related QT interval prolongation and associated proarrhythmic risk, offering essential evidence for preclinical safety assessment.[87] In regenerative medicine and transplantation research, functional organoids display considerable therapeutic potential. Vascularized liver organoids, for instance, represent a novel approach for treating liver cirrhosis by supporting hepatic tissue regeneration and restoring physiological function.[86] Intestinal organoids have likewise demonstrated efficacy in repairing intestinal function in patients with short bowel syndrome, improving nutrient absorption and digestive capacity.[87] Fundamental mechanistic studies also benefit substantially from organoid systems, exemplified by Alzheimer's disease-associated brain organoids that recapitulate β-amyloid plaque deposition and provide powerful platforms for dissecting neurodegenerative disease mechanisms.[87]

Finally, classification based on technological integration and storage modality delineates organoid biobanks into physical repositories and digital data infrastructures. Physical biobanks consist primarily of cryopreserved, viable organoid specimens maintained in liquid nitrogen or ultralow-temperature freezers to ensure long-term genetic stability by suppressing metabolic activity and preventing genomic instability.[22] Internationally, several mature physical biobanking infrastructures have set industry benchmarks for standardized construction and open sharing. HUB Organoids has established a full-process standardized pipeline from tissue collection, organoid generation, and quality validation, to cryopreservation and distribution, covering gastrointestinal tumors, breast cancer, and rare disease models, and is recognized as the gold-standard reference for PDO biobanking.[17] HCMI (hosted by ATCC) implements uniform quality control criteria for all deposited organoid models, including genomic identity verification, histological matching with primary tissues, and functional validation, ensuring high reproducibility of research results across independent institutions.[22] The Wellcome Sanger Institute Tumor Organoid Biobank further integrates large-scale whole-genome sequencing data with organoid drug sensitivity profiles, building a coupled resource of biological samples and multi-dimensional omics information to support precision oncology and drug discovery research.[7]

In parallel, digital organoid databases integrate clinical annotations and multi-omic datasets, including pathological classification, genomic mutation landscapes, and therapeutic responses. These data resources enable large-scale computational analyses and AI-driven modeling to uncover latent disease associations and support evidence-based clinical decision-making. Integration of single-cell sequencing, proteomics, and spatial omics further enables high-resolution dissection of organoid molecular states across physiological and pathological contexts. Collectively, this multi-dimensional biobanking architecture enhances the functional scope of organoid resources and establishes a reliable basis for precision medicine and individualized therapeutic strategies.

4. Core application scenarios of organoid biobanks: From fundamental research to clinical translation

Leveraging the unique biological fidelity and scalability, organoid biobanks have demonstrated extensive and diverse applications across multiple cutting-edge fields in biomedical research. Their principal applications encompass cancer research, genetic disease modeling, infectious disease investigation, regenerative medicine and organ repair, drug discovery and toxicity assessment, developmental biology, and environmental and public health research (Figure 6E).[86]

Organoid biobanks provide critical support for anticancer drug screening and precision oncology. By recapitulating the complex tumor microenvironment of patients and retaining the original tumor's genotypic and phenotypic characteristics, organoids constitute highly reliable experimental models for predicting therapeutic responses.[88] In a representative study, Hu *et al.*[89] combined patient-derived lung cancer organoids with a microwell array-based drug-testing platform, enabling rapid functional profiling of individualized therapeutic responses within a week. The resulting drug sensitivity profiles were consistent with tumor genomic alterations, patient-derived xenograft responses, and clinical treatment

outcomes, demonstrating the value of organoid-based functional assays for guiding individualized treatment selection (Figure 7A). This example highlights how systematic organoid drug-response profiling can provide clinically relevant evidence for precision oncology beyond conventional genomic prediction alone. Intratumoral heterogeneity remains a central challenge in oncology research, particularly for understanding tumor evolution, suppressive mechanisms, and therapeutic resistance. Organoid biobanks offer a distinct advantage by preserving tumor heterogeneity at both genetic and phenotypic levels, which is essential for elucidating tumor initiation, progression, and mechanisms of therapeutic resistance.[90] For instance, colorectal cancer organoid biobanks, integrated with multi-dimensional analyses—including whole-exome sequencing, copy number variation profiling, histopathological characterization, and drug screening—enable comprehensive and systematic dissection of tumor-intrinsic features. This makes them an indispensable platform for addressing the complexities of intratumoral heterogeneity.[91]

The significance of organoid biobanks is particularly evident in genetic disease research, where they contribute substantially to disease modeling, mechanistic investigations, and the assessment of gene therapies. PDOs offer invaluable resources for capturing disease phenotypes and serve as key tools for identifying disease-associated genes and elucidating phenotypic heterogeneity.[87] In cystic fibrosis, Maule *et al.*[92] used patient-derived intestinal organoids to evaluate allele-specific repair of *CFTR* splicing mutations through an AsCas12a-mediated genome-editing approach. Functional correction was demonstrated by the restoration of *CFTR*-dependent forskolin-induced swelling in edited organoids and was further validated in airway epithelial cells, highlighting the utility of organoids as clinically relevant platforms for assessing gene-editing therapies (Figure 7B). Similarly, liver organoids derived from patients with Alagille syndrome have been shown to recapitulate disease-associated bile duct developmental abnormalities, further validating the value of organoids in genetic disease research.[93] These investigations deepen understanding of disease pathophysiology and lay the groundwork for the development of novel therapeutic approaches.

For the evaluation of gene therapy efficacy and safety, organoid biobanks serve as ideal experimental platforms. Advanced genome-editing technologies enable precise introduction or correction of disease-causing mutations within organoids, allowing systematic assessment of phenotypic rescue.[94] In Duchenne muscular dystrophy (DMD), antisense oligonucleotide (ASO)-mediated exon correction in organoid models successfully restored dystrophin expression, offering compelling support for the clinical translation of gene therapies for DMD. These advances underscore the pivotal role of organoid biobanks in driving personalized and precision medicine.

Organoid biobanks also exhibit substantial potential in infectious disease research, particularly in elucidating virus–host interactions and enabling antiviral drug screening and therapeutic strategy evaluation. As physiologically relevant models, organoids provide powerful systems for investigating viral infection dynamics and host cellular responses, thereby opening new avenues for antiviral drug development.[95] During the COVID-19 pandemic, organoid models were extensively employed to characterize SARS-CoV-2 infection mechanisms and evaluate therapeutic interventions, yielding critical experimental evidence for the global pandemic response.[14] Human lung organoids have further been used to assess the impacts of emerging variants on host immune responses and identify effective antiviral agents[96], establishing a dual platform for efficacy and safety evaluation that accelerates clinical translation in infectious disease therapeutics.

Regenerative medicine applications illustrate the translational arc from laboratory innovation to clinical intervention. A landmark achievement by Sugimoto *et al.*[97] at Keio University constructed transplantable intestinal mucosa using an innovative "small intestine-ized colon" strategy, whereby ileum-derived organoids replaced colonic epithelium with small intestinal epithelium possessing functional characteristics, thereby reconstructing absorptive functions for lipid, carbohydrate, and peptide uptake and significantly improving survival in rat models of short bowel syndrome. This approach demonstrates how organoid biobanks can bridge the gap between *in vitro* modeling and functional tissue replacement.

Organoid biobanks provide novel strategies for regenerative medicine and transplantation-related tissue repair. By preserving expandable and functionally competent tissue structures, organoid resources offer promising platforms for restoring damaged tissues and evaluating regenerative interventions. In a representative study, Zhang *et al.*[98] showed that transplantation of intestinal organoids attenuated intestinal ischemia/reperfusion injury in mice, improved survival outcomes, and promoted intestinal mucosal repair. Mechanistically, transplanted organoids secreted L-malic acid, which induced M2 macrophage polarization and restored IL-10 levels through a suppressor of cytokine signaling 2-dependent pathway, thereby reshaping the local immune microenvironment and supporting tissue regeneration (Figure 7C). These findings highlight the therapeutic potential of organoid transplantation as a regenerative strategy for repairing acute tissue injury and provide experimental support for future development of organoid-based regenerative therapies.

For drug development, organoid biobanks have become powerful platforms for high-throughput compound screening. They support rapid, reliable assessment of candidate agents for antitumor activity and off-target effects, greatly streamlining the entire drug discovery process.[86] Tumor organoid models are now widely applied in large-scale screening platforms and have become indispensable tools for identifying novel anticancer agents. PDOs preserve tumor morphology, genetic features, and biomarker expression, allowing accurate prediction of therapeutic responses and positioning them as ideal models for personalized drug screening and precision oncology.[87]

Organoid biobanks are equally indispensable for drug toxicity assessment. Liver organoids provide reliable evaluation of hepatotoxicity, while cardiac organoids enable effective assessment of cardiotoxic effects.[88] As human-relevant *in vitro* models, these platforms support early safety profiling, facilitate timely recognition of compound-related toxicities, and may improve the efficiency of preclinical drug development. Tan *et al.*[99] developed DILITracer, an AI-based model for predicting drug-induced liver injury (DILI) severity from bright-field images of human liver organoids. By integrating spatiotemporal and *z*-axis imaging information from organoids exposed to compounds classified by the FDA DILIrank database, this model linked dynamic organoid morphology with hepatotoxicity severity and achieved ternary classification of No-, Less-, and Most-DILI concern compounds with an overall accuracy of 82.34% (Figure 7D).

In developmental biology research, organoid biobanks provide ideal experimental systems for probing organogenesis. Cardiac organoids, for instance, closely recapitulate embryonic heart development and offer powerful platforms for dissecting key regulatory steps and molecular mechanisms governing cardiogenesis (Figure 7E).[100] These models advance understanding of heart development and also inform preventive and therapeutic strategies for congenital heart diseases. Beyond developmental research, organoid biobanks greatly facilitate mechanistic exploration of human diseases. By engineering organoids harboring specific disease-associated genetic mutations, researchers can systematically investigate how these alterations disrupt normal development and organ function, thereby uncovering critical pathogenic mechanisms and informing targeted therapeutic development.

Beyond biomedical applications, organoid biobanks are emerging as valuable tools in environmental health research. Liver organoids recapitulate dose-dependent toxic effects of environmental contaminants such as perfluorooctane sulfonate and uncover synergistic hepatotoxicity caused by exposure to microplastics combined with bisphenol A. Intestinal organoid models demonstrate that heavy metals disrupt mucus secretion via Notch signaling, while antibiotics impair neonatal intestinal epithelial barrier defense. These findings illustrate organoids' potential to bridge environmental toxicology and mechanistic pathology, providing experimentally grounded evidence for environmental protection policies and public health intervention. Lung organoid models applied in occupational exposure studies have substantially enhanced respiratory health risk assessment, clarified molecular mechanisms of environmental lung diseases, and supported the development of targeted preventive strategies. Together with other organ-specific models, these applications position organoid biobanks as innovative methodological platforms for exposure evaluation that complement traditional epidemiological approaches.

5. Standardization challenges and pathways to breakthroughs in organoid biobanks

Current organoid research is severely hampered by the lack of unified standards, forming a core bottleneck that restricts large-scale expansion and hinders clinical translation. Major deficits remain in technical workflows, quality management, and cross-laboratory data harmonization, collectively weakening the reproducibility and cross-site comparability of organoid-based experiments. Such limitations greatly constrain the broader application of organoid platforms in precision medicine and high-throughput drug screening. Future progress relies on in-depth mechanistic exploration and continuous technical advances to build mature, universal standardization systems, which will drive systematic progress across the entire organoid research field.[49]

In response, a series of consensus guidelines have been issued covering the generation, culture, quality control, and translational use of diverse organoid subtypes (Table 2). These frameworks provide evidence-based specifications for cell sourcing, culture regimens, and phenotypic validation, aiming to sustain stable organoid quality and ensure clinical relevance. Importantly, tissue-specific standardization systems have been established: tumor organoid protocols define tissue dissociation, medium formulation, and growth factor supplementation to preserve intrinsic heterogeneity[101]; liver organoid standards specify differentiation protocols and functional assessment criteria (albumin secretion, drug-metabolizing enzyme activity)[102]; and mature quality control systems now incorporate multi-dimensional evaluation covering morphology, biomarker identification, functional verification, and genetic stability detection.[103] Standards governing organoid quality control, preservation, and storage further facilitate the transition of organoid technologies from the bench to the bedside, enhancing their operational feasibility and reproducibility.[103]

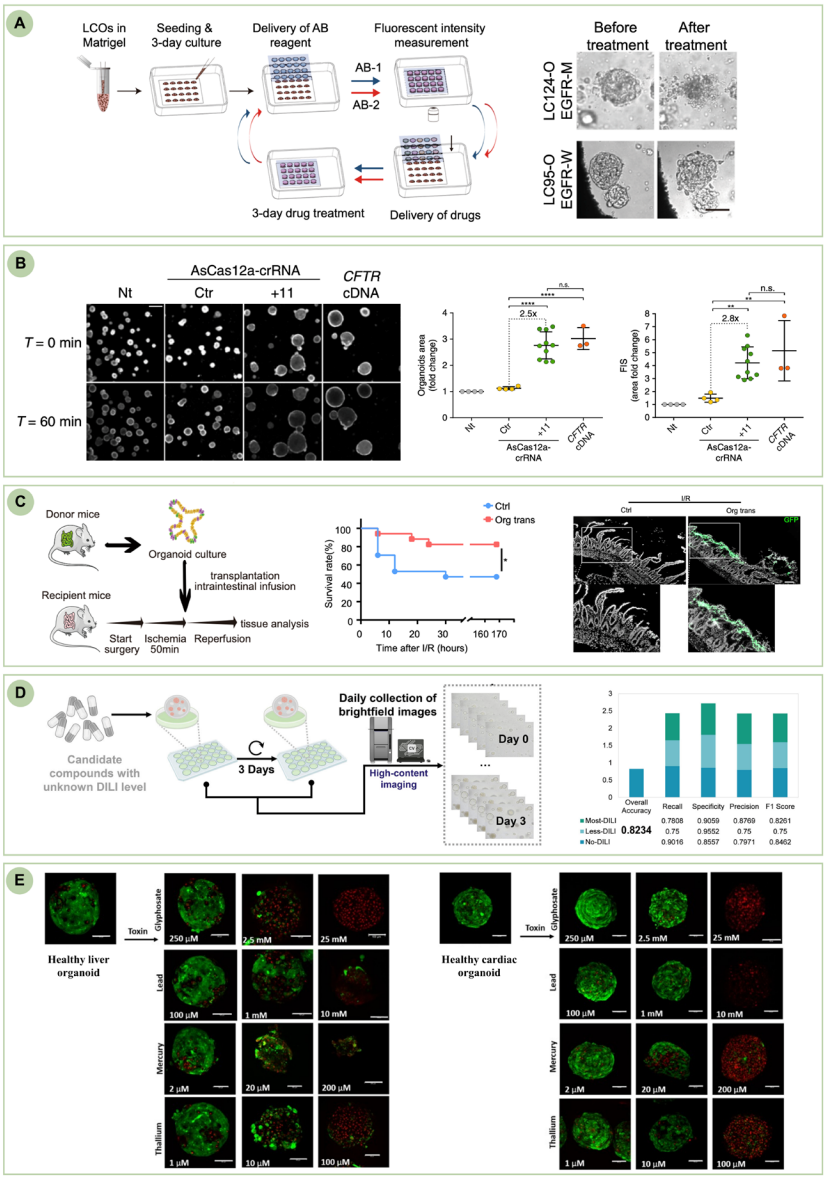

Figure 7. Organoid biobanks support a wide spectrum of biomedical research applications. (A) Patient-derived lung cancer organoids were analyzed on an integrated microwell array chip, enabling rapid assessment of drug response. Gefitinib selectively inhibited EGFR-mutant organoids but not EGFR wild-type organoids, demonstrating the potential of organoid-based assays for individualized treatment selection. Adapted from Hu *et al.*[89] (B) Functional restoration of CFTR activity in intestinal organoids derived from patients with cystic fibrosis after AsCas12a-mediated genome editing. Representative calcein-labeled organoid images and quantitative forskolin-induced swelling assays show that AsCas12a-crRNA+11 editing of the CFTR 3272-26A>G splicing mutation restored CFTR-dependent organoid swelling responses in organoids, with functional recovery comparable to CFTR cDNA delivery. Adapted from Maule *et al.*[92] (C) Therapeutic effect of intestinal organoid transplantation in intestinal ischemia/reperfusion injury. The experimental workflow shows organoid transplantation after intestinal ischemia/reperfusion injury. Kaplan–Meier analysis demonstrated improved survival in organoid-transplanted mice, and representative fluorescence images confirmed engraftment of transplanted organoids into the injured small intestinal mucosa 36 h post-injury. Adapted from Zhang *et al.*[98] (D) Artificial intelligence-assisted hepatotoxicity prediction using bright-field images of human liver organoids. The schematic shows the application of DILITracer for predicting the drug-induced liver injury risk of compounds with unknown hepatotoxicity from human liver organoid bright-field image sequences. Model performance metrics, including accuracy, recall, specificity, precision, and F1 score, support the feasibility of image-based ternary classification of No-, Less-, and Most-DILI concern compounds. Adapted from Tan *et al.*[99] (E) Visual assessment of environmental toxicant-induced effects on cardiac organoids using live/dead cell assays. Ethidium homodimer staining marks dead cells (red), whereas calcein AM staining labels viable cells (green), revealing the effects of glyphosate, lead, mercury, and thallium on cardiac organoids. Adapted from Forsythe *et al.*[100]

Abbreviations: AB: Assay buffer; AsCas12a: *Acidaminococcus* sp. Cas12a CRISPR enzyme; CFTR: Cystic fibrosis transmembrane conductance regulator; cDNA: Complementary deoxyribonucleic acid; Ctr: Control; DILI: Drug-induced liver injury; EGFR: Epidermal growth factor receptor; FIS: Forskolin-induced swelling; GFP: Green fluorescent protein; I/R: Ischemia/reperfusion; LCOs: Lung cancer organoids; n.s.: Not significant; Nt: No treatment.

The introduction of such standardized guidelines has profound implications for the large-scale clinical implementation of organoid technologies. In drug sensitivity testing, standardized operational procedures and unified criteria for result interpretation enable cross-institutional data comparability, thereby providing reliable evidence for personalized treatment selection.[104] The adoption of these frameworks substantially improves the credibility and clinical applicability of organoid-based decision-making tools.[105] With further advances in mechanistic research, the formulation of internationally recognized consensus standards, and large-scale multicenter validation, organoid technology will serve as a vital translational bridge connecting fundamental biomedical research with clinical practice.

5.1. Technical considerations: Cryopreservation and recovery protocols and culture consistency

Despite significant advancements in biomedical applications, organoid technologies remain hindered by substantial standardization challenges—most notably in cryopreservation and recovery protocols and the maintenance of culture consistency. A key limitation in cryopreservation and recovery is structural damage induced by ice crystals, which impairs functional integrity post-thaw. Conventional slow-rate freezing (≈−1°C/min) in liquid nitrogen frequently triggers intracellular ice formation, disrupting cellular membranes and limiting post-thaw viability of PDOs to below 60%.[106]

In contrast, vitrification-based cryopreservation markedly improves post-thaw survival rates to above 80%; however, this approach necessitates high-dose cryoprotectants, such as 20% dimethyl sulfoxide, which induces osmotic stress. In liver organoids, this stress suppresses urea synthesis by approximately 25 ± 3%.[107] Supplementing cryoprotectant cocktails with 0.5 mol/L trehalose represents an effective strategy to alleviate osmotic injury, recovering urea synthesis function in resuscitated liver organoids to more than 90% of baseline levels.[107] Furthermore, automated cryopreservation platforms capable of ultra-rapid cooling (rates of up to −2,000°C/min during vitrification) greatly reduce manual operational errors. This standardized cooling control lowers experimental variability and strengthens the overall reproducibility and reliability of organoid cryopreservation workflows.[108]

Culture consistency represents another critical determinant of reproducible organoid expansion, with batch-to-batch variability constituting a major source of experimental variation. ECM composition strongly influences organoid formation efficiency. Batch discrepancies in conventional Matrigel may cause organoid formation rates to vary by up to 30%, while chemically defined alternatives such as VitroGel limit such variation to below 10%. Variability in soluble signaling factors likewise distorts organoid proliferation kinetics. Even minor shifts in EGF levels (±10 ng/mL) can alter proliferative activity by approximately 20%.[109] To enhance culture stability, the use of high-purity (>95%) recombinant proteins with concentration verification by enzyme-linked immunosorbent assay is recommended to reduce variability arising from inconsistent factor dosing.

Beyond chemical and biomaterial optimization, the integration of automated culture and monitoring systems—such as Incucyte platforms—enables real-time assessment of organoid growth dynamics. By dynamically quantifying organoid morphology and dimensions, these systems further promote standardization and normalization of culture conditions, providing critical technical support for maintaining culture consistency.[110]

5.2. Quality control frameworks: Genetic and functional stability assessment

Genetic and functional stability serve as the core quality control indicators that ensure the reliability and reproducibility of organoid biobanks. Comprehensive genomic profiling is required to monitor genome integrity during long-term culture expansion. Regular karyotypic screening is therefore advised every 10 passages. G-banding staining and single nucleotide polymorphism array profiling enable accurate surveillance of chromosomal ploidy and genomic structural stability, restricting the overall chromosomal aberration rate to below 5%.[111–113]

In addition to genetic stability, the growing use of multi-omics technologies requires quality control to be extended to the assessment of analyte-level stability. As emphasized in recent regulatory and standardization frameworks for pre-analytical procedures, the reliability of molecular diagnostics depends not only on the integrity of the biospecimen itself but also on the preservation of downstream analytes, including RNA, proteins, and metabolites. Therefore, organoid biobanks should define and document analyte-specific pre-analytical variables, including collection-to-processing intervals, transport conditions, storage temperature and duration, passage number, cryopreservation and recovery procedures, and the number of freeze–thaw cycles. For transcriptomic applications, RNA integrity, transcriptomic concordance with parental tissues, and passage-associated expression changes should be monitored. For proteomic and secretome-based studies, tissue-specific protein expression, post-translational modification profiles, and key functional proteins should be preserved. For metabolomic analyses, standardized quenching, extraction, and storage procedures are required to minimize metabolic degradation and metabolic drift. Such analyte-oriented quality control

is essential to ensure that organoid resources remain fit for their intended use in multi-omics integration, biomarker discovery, drug-response modeling, and clinical translation.[114]

For the surveillance of key oncogenic driver mutations, including *KRAS*, *EGFR*, and *TP53*, digital polymerase chain reaction has become a highly sensitive analytical tool. This technique achieves high detection sensitivity with a limit of 0.1% variant allele frequency, and shortens assay turnaround time to approximately 24 h, making it well suited for high-throughput biobank operations.[115] In addition, Assay for Transposase-Accessible Chromatin with high-throughput sequencing can be applied to assess chromatin accessibility, enabling evaluation of epigenetic concordance between organoids and primary tissues and ensuring similarity levels exceeding 85%.[116,117]

Functional stability assessment requires organoid-type-specific performance metrics. For intestinal organoids, commonly used indicators include barrier permeability (e.g., fluorescein isothiocyanate-dextran permeability < 1%/h) and villus architecture integrity (e.g., villus height of 100–150 μm).[118,119] For liver organoids, core functional parameters include cytochrome P450 enzyme activity (CYP3A4 >10 pmol/min/mg protein) and urea synthesis rates (>5 μg/[10^6 cells·24 h]).[120] Cardiac organoid functionality can be assessed using patch-clamp techniques to measure action potential duration (APD90 of 200–300 ms) and calcium transient amplitude ($F/F_0 > 2.0$), ensuring electrophysiological fidelity.[121]

To balance quality control costs with operational feasibility, the establishment of a "minimal quality control panel" is recommended. This panel prioritizes the most representative and functionally informative parameters for each organoid type, thereby maintaining data reliability while improving efficiency.[20,122,123] Such an approach optimizes resource utilization and provides a pragmatic, scalable standard for quality control across diverse organoid platforms.

5.3. Data integration: Format harmonization and privacy protection

During the development and implementation of organoid biobanks, data fragmentation has become increasingly evident, manifesting as heterogeneous data formats, cross-platform integration challenges, and tensions between data sharing and privacy protection. Addressing these issues requires coordinated advances in data format standardization, system integration architecture, and privacy-preserving strategies.[124]

Data heterogeneity represents a fundamental cause of widespread data fragmentation. At present, diverse data categories follow independent coding rules and naming specifications. Clinical pathological classifications generally adopt the International Classification of Diseases (11th Revision) coding system, experimental drug sensitivity results are annotated based on the National Cancer Institute Thesaurus terminology, and multi-omics profiles such as single-cell RNA sequencing datasets are organized in accordance with the FAIR guidelines (Findable, Accessible, Interoperable, Reusable). The absence of unified standards severely hinders data interoperability and reduces overall analytical efficiency. To overcome such technical barriers, a cross-platform data integration framework is urgently required. The adoption of HL7 Fast Healthcare Interoperability Resources-based standardized interfaces enables seamless integration and information exchange across electronic medical record, laboratory information, and biobank management systems (BMS). Such integrated architectures are projected to improve overall data processing efficiency by nearly 40%. Meanwhile, standardized operating procedures should be fully enforced to regulate data entry and sharing protocols, harmonize data formatting criteria, and further enhance the cross-system compatibility and operational utility of biobank datasets.[124]

As organoid biobanks are increasingly applied in clinical research, balancing data sharing with privacy protection has become a pressing challenge.[125] To protect patient confidentiality while meeting research demands, a "de-identification and tiered access" strategy is recommended. Identifiable information (e.g., names and identification numbers) should be removed, while retaining key research-relevant attributes such as age, sex, and pathological stage, where appropriate. De-identified datasets can then be shared under tiered access controls, allowing research teams to access data according to defined authorization levels, thereby maximizing data utility while minimizing privacy risks.

In terms of data-sharing infrastructure, blockchain technology represents a promising solution. Blockchain-based distributed data platforms enable cryptographic protection at each data node, ensuring data security and privacy.[126] Moreover, the immutability of blockchain records guarantees transparency and traceability of data access, enhancing data integrity and trustworthiness. This decentralized architecture complies with regulations such as China's Regulations on the Administration of Human Genetic Resources and the European Union's General Data Protection Regulation, enabling secure and compliant data-sharing channels for multicenter research collaborations[127] (Table 2).

6. Conclusion and future perspectives

Organoid biobanks, featuring high biomimetic potential and strong clinical relevance, have emerged as strategic

Table 2. The timelines of organoid-related standards or guidelines

ID number	Standard title	Issuing organization	Publication date
T/CMBA017-2022	Guideline of construction and preservation of organoids of gastrointestinal epithelial tissues	China Medicinal Biotech Association	March 2022
–	Expert consensus of clinical application about tumor precision therapy guided by organoid-based drug sensitivity testing	–	June 2022
–	Chinese experts consensus on quality control standards for tumor organoids diagnosis and treatment platform	–	June 2022
T/SHSYCXH12-2022	Technical specification for culture of patient-derived lung cancer organoids	Shanghai Society of Genetics	September 2022
T/SHDSGY167-2023	Technical specification for the construction of brain tumor organoid models	Shanghai DuShiGongYe Association	December 2022
T/CMBA020-2023	Guideline for preparation, cryopreservation, recovery, and identification of organoids of human normal breast and breast cancer tissue	China Medicinal Biotech Association	February 2023
T/CRHA019-2023	Guidelines for the establishment, quality control, and storage of human hepatobiliary tumor organoids	Chinese Research Hospital Association	June 2023
T/CRHA020-2023	Guidelines for the establishment, quality control, and storage of biliary epithelial tissue organoids	Chinese Research Hospital Association	June 2023
T/CRHA018-2023	Guidelines for the establishment, quality control, and storage of human hepatic progenitor cell derived organoids	Chinese Research Hospital Association	June 2023
–	Standard: Human intestinal organoids	–	June 2023
–	Standard: Human intestinal cancer organoids	–	June 2023
–	Guidelines for manufacturing and application of organoids: Lung	–	May 2024
–	Guidelines for manufacturing and application of organoids: Skin	–	May 2024
–	Guidelines for manufacturing and application of organoids: Heart	–	May 2024
T/QMHIPA 001-2024	Culture and identification of patient-derived organoids for intrahepatic cholangiocarcinoma	Qingdao Medical and Health Industry Promotion Association	Mar 2024
T/CSCB 0023-2024	Human gastric organoids	Chinese Society for Cell Biology	December 2024
T/CSCB 0030-2024	Human cerebral organoids	Chinese Society for Cell Biology	December 2024
T/FDSA 0074-2025	Guideline for construction of human breast cancer organoids and drug sensitivity testing	Food and Drug Safety Promotion Association of China	April 2025

Notes: All coded standards adopt the format T/Abbreviation–Serial Number–Year, where "T" indicates a group standard, the alphabetic segment represents the issuing organization's English or Pinyin abbreviation, the numeric serial number represents the sequence of standards released by the issuing institution, and the four-digit number refers to the publication year. Seven entries marked "–" are expert consensus and technical guidance documents (two tumor organoid consensus documents in 2022, two intestinal organoid specifications in 2023, and three organ manufacturing and application guidelines in 2024) compiled by professional academic committees and expert working groups. Published as academic papers or association announcements to provide timely technical guidance, they are not officially registered group standards governed by the Administrative Measures for Group Standards and thus lack formal standard IDs.

research platforms in modern biomedical research. They encompass a complete technological pipeline, covering cell sourcing, organoid generation, long-term cryopreservation, and data management.[22] Their translational value is prominently reflected across multiple research and clinical domains: in tumor precision medicine, they support personalized drug sensitivity testing[85]; in pharmaceutical development, they enable high-throughput compound screening[111]; and in regenerative medicine, they facilitate tissue replacement and functional restoration.[128] Currently, the field of organoid biobanking is undergoing a critical transition from laboratory-scale innovation to industrial-scale production and clinical application. Systematic standardization and interdisciplinary integration—encompassing bioengineering, computational biology, and clinical medicine—are the core driving forces behind sustainable development in this field.[45]

Three technological frontiers are poised to reshape organoid biobanking in the next decade. First, engineered vascularization—fabricating artificial vascular networks

via two-photon 3D printing—may increase organoid vascularization efficiency to approximately 35%, markedly improving structural integrity and functional maturation.[129] Second, immune microenvironment reconstruction through iPSC-derived immune cell co-culture with tumor organoids enhances physiological relevance and improves predictive accuracy for immunotherapy assessment.[130] Third, deep learning-based multi-omics integration can automatically optimize culture media formulations, substantially accelerating organoid maturation while improving efficiency and reproducibility.[45] Together, these advances signal organoid biobanks' evolution from alternative experimental models into robust predictive systems that will become important platforms for advancing precision medicine and drug discovery.

From a standardization perspective, developing and implementing national and industry-specific guidelines is essential for normalizing and scaling up organoid technologies.[22] These guidelines should clearly outline requirements for cell source selection and quality control, standardized culture protocols, and data governance—key pillars for ensuring consistency and reliability across applications. In addition, the establishment of cross-institutional sharing infrastructures, such as a "National Organoid Resource Bank," would enable cross-regional sharing of both biological specimens and associated datasets, thereby maximizing resource utilization and reducing redundancy.[22] Alignment with international standards represents another critical priority, facilitating global collaboration, data interoperability, and cross-border translational research.[22]

Clarification of industrialization pathways will further promote the widespread application of organoid technologies. Establishing specialized clinical translation platforms is anticipated to unlock the full clinical potential of organoid biobanks, thereby advancing precision medicine and facilitating personalized treatment decision-making.[105] Concurrently, the maturation of an integrated industrial ecosystem—including reagent development, automated culture and screening equipment, and downstream clinical services—will accelerate commercialization and enhance market competitiveness.[111] With the continued refinement of ethical oversight and regulatory frameworks, the sustainable development of organoid technologies can be ensured, enabling broad application while rigorously safeguarding patient privacy and ethical compliance.[131,132]

Driven by coordinated policy support and continuous technological advances, organoid biobanks are expected to evolve over the next 5–10 years from "alternative experimental models" into robust "predictive systems," ultimately becoming key platforms supporting precision medicine and drug discovery.[22] This transformative shift is expected to revolutionize biomedical research, spurring major breakthroughs in personalized therapy and translational drug development.

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Conflict of interest

The authors declare no conflict of interest.

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Not applicable.

Consent for publication

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Availability of data

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References

1. Rossi G, Manfrin A, Lutolf MP. Progress and potential in organoid research. *Nat Rev Genet*. 2018;19(11):671-687.
doi: 10.1038/s41576-018-0051-9

2. Fatehullah A, Tan SH, Barker N. Organoids as an in vitro model of human development and disease. *Nat Cell Biol*. 2016;18(3):246-254.
doi: 10.1038/ncb3312

3. Lancaster MA, Knoblich JA. Organogenesis in a dish: Modeling development and disease using organoid technologies. *Science*. 2014;345(6194):1247125.
doi: 10.1126/science.1247125

4. Ingber DE. Reverse Engineering Human Pathophysiology with Organs-on-Chips. *Cell*. 2016;164(6):1105-1109.
doi: 10.1016/j.cell.2016.02.049

5. Spence JR, Mayhew CN, Rankin SA, *et al*. Directed differentiation of human pluripotent stem cells into intestinal

tissue in vitro. *Nature*. 2010;470(7332):105-109.

doi: 10.1038/nature09691

6. Lancaster MA, Renner M, Martin CA, *et al*. Cerebral organoids model human brain development and microcephaly. *Nature*. 2013;501(7467):373-379.

doi: 10.1038/nature12517

7. Vlachogiannis G, Hedayat S, Vatsiou A, *et al*. Patient-derived organoids model treatment response of metastatic gastrointestinal cancers. *Science*. 2018;359(6378):920-926.

doi: 10.1126/science.aao2774

8. Pauli C, Hopkins BD, Prandi D, *et al*. Personalized In Vitro and In Vivo Cancer Models to Guide Precision Medicine. *Cancer Discov*. 2017;7(5):462-477.

doi: 10.1158/2159-8290.CD-16-1154

9. Sato T, Vries RG, Snippert HJ, *et al*. Single Lgr5 stem cells build crypt-villus structures in vitro without a mesenchymal niche. *Nature*. 2009;459(7244):262-265.

doi: 10.1038/nature07935

10. Eiraku M, Takata N, Ishibashi H, *et al*. Self-organizing optic-cup morphogenesis in three-dimensional culture. *Nature*. 2011;472(7341):51-56.

doi: 10.1038/nature09941

11. Takebe T, Sekine K, Enomura M, *et al*. Vascularized and functional human liver from an iPSC-derived organ bud transplant. *Nature*. 2013;499(7459):481-484.

doi: 10.1038/nature12271

12. Sachs N, Papaspyropoulos A, Zomer-van Ommen DD, *et al*. Long-term expanding human airway organoids for disease modeling. *EMBO J*. 2019;38(4).

doi: 10.15252/embj.2018100300

13. Nguyen TA, Jo MH, Choi YG, *et al*. Functional Anatomy of the Human Microprocessor. *Cell*. 2015;161(6):1374-1387.

doi: 10.1016/j.cell.2015.05.010

14. Kim J, Koo BK, Knoblich JA. Human organoids: model systems for human biology and medicine. *Nat Rev Mol Cell Biol*. 2020;21(10):571-584.

doi: 10.1038/s41580-020-0259-3

15. Thran M, Mukherjee J, Pönisch M, *et al*. mRNA mediates passive vaccination against infectious agents, toxins, and tumors. *EMBO Mol Med*. 2017;9(10):1434-1447.

doi: 10.15252/emmm.201707678

16. Kelley MW. Generation of Human Hair Cells In Vitro: Is It All about How the Wnt Blows? *Cell Stem Cell*. 2017;21(1):11-12.

doi: 10.1016/j.stem.2017.06.007

17. van de Wetering M, Francies HE, Francis JM, *et al*. Prospective derivation of a Living Organoid Biobank of colorectal cancer patients. *Cell*. 2015;161(4):933-945.

doi: 10.1016/j.cell.2015.03.053

18. Corsini NS, Peer AM, Moeseneder P, *et al*. Coordinated Control of mRNA and rRNA Processing Controls Embryonic Stem Cell Pluripotency and Differentiation. *Cell Stem Cell*. 2018;22(4):543-558.e12.

doi: 10.1016/j.stem.2018.03.002

19. Broutier L, Mastrogiovanni G, Verstegen MMA, *et al*. Human Primary Liver Cancer -derived Organoid Cultures for disease modelling and drug screening. *Nat Med*. 2017;23(12):1424-1435.

doi: 10.1038/nm.4438

20. Xie X, Li X, Song W. Tumor organoid biobank-new platform for medical research. *Sci Rep*. 2023;13(1).

doi: 10.1038/s41598-023-29065-2

21. Bacci M, Lorito N, Ippolito L, *et al*. Reprogramming of Amino Acid Transporters to Support Aspartate and Glutamate Dependency Sustains Endocrine Resistance in Breast Cancer. *Cell Rep*. 2019;28(1):104-118.e8.

doi: 10.1016/j.celrep.2019.06.010

22. Di Paola FJ, Calafato G, Piccaluga PP, Tallini G, Rhoden KJ. Patient-Derived Organoid Biobanks for Translational Research and Precision Medicine: Challenges and Future Perspectives. *J Pers Med*. 2025;15(8):394.

doi: 10.3390/jpm15080394

23. Roerink SF, Sasaki N, Lee-Six H, *et al*. Intra-tumour diversification in colorectal cancer at the single-cell level. *Nature*. 2018;556(7702):457-462.

doi: 10.1038/s41586-018-0024-3

24. Ooft SN, Weeber F, Dijkstra KK, *et al*. Patient-derived organoids can predict response to chemotherapy in metastatic colorectal cancer patients. *Sci Transl Med*. 2019;11(513).

doi: 10.1126/scitranslmed.aay2574

25. Thomas SC, Miller G, Li X, Saxena D. Getting off tract: contributions of intra-organ microbiota to cancer in extra-intestinal organs. *Gut*. 2023;73(1):175-185.

doi: 10.1136/gutjnl-2022-328834

26. Frank S, Ahuja G, Bartsch D, *et al*. yylncT Defines a Class of Divergently Transcribed lncRNAs and Safeguards the T-mediated Mesodermal Commitment of Human PSCs. *Cell Stem Cell*. 2019;24(2):318-327.e8.

doi: 10.1016/j.stem.2018.11.005

27. Lee SH, Hou JC, Hamidzadeh A, *et al*. A molecular clock controls periodically driven cell migration in confined spaces. *Cell Syst*. 2022;13(7):514-529.e10.

doi: 10.1016/j.cels.2022.05.005

28. Aria M, Cuccurullo C. *bibliometrix*: An R-tool for comprehensive science mapping analysis. *J Informetr*. 2017;11(4):959-975.

doi: 10.1016/j.joi.2017.08.007

29. Docampo D. Erratum to: On using the Shanghai ranking to assess the research performance of university systems. *Scientometrics*. 2010;86(1):237-237.

doi: 10.1007/s11192-010-0315-4

30. Moed HF. *Citation Analysis in Research Evaluation*. Vol 9. Springer-Verlag; 2005.

doi: 10.1007/1-4020-3714-7

31. Bar-Ilan J. Which h-index? — A comparison of WoS, Scopus and Google Scholar. *Scientometrics*. 2007;74(2):257-271.

doi: 10.1007/s11192-008-0216-y

32. Chen C. CiteSpace II: Detecting and visualizing emerging trends and transient patterns in scientific literature. *J Am Soc Inf Sci Technol*. 2005;57(3):359-377.

doi: 10.1002/asi.20317

33. Small H. Co-citation in the scientific literature: A new measure of the relationship between two documents. *J Am Soc Inf Sci*. 1973;24(4):265-269.

doi: 10.1002/asi.4630240406

34. Nikolov D, Lalmas M, Flammini A, Menczer F. Quantifying Biases in Online Information Exposure. *J Assoc Inf Sci Technol*. 2018;70(3):218-229.

doi: 10.1002/asi.24121

35. Lubango LM, Pouris A. Industry work experience and inventive capacity of South African academic researchers. *Technovation*. 2007;27(12):788-796.

doi: 10.1016/j.technovation.2007.05.013

36. Gu Z, Gu L, Eils R, Schlesner M, Brors B. *circlize* implements and enhances circular visualization in R. *Bioinformatics*. 2014;30(19):2811-2812.

doi: 10.1093/bioinformatics/btu393

37. Gu Z, Eils R, Schlesner M. Complex heatmaps reveal patterns and correlations in multidimensional genomic data. *Bioinformatics*. 2016;32(18):2847-2849.

doi: 10.1093/bioinformatics/btw313

38. Rinne M. Technology roadmaps: Infrastructure for innovation. *Technol Forecast Soc Change*. 2004;71(1):67-80.

doi: 10.1016/j.techfore.2003.10.002

39. Di Paco G, Meoni G, Ghini V, *et al*. Recent trends in metabolomics by NMR spectroscopy. *Angew Chem Int Ed*. 2026;65(24).

doi: 10.1002/anie.202525689

40. Li H, Liu H, Chen K. Living biobank-based cancer organoids: prospects and challenges in cancer research. *Cancer Biol Med*. 2022;19(7):965-982.

doi: 10.20892/j.issn.2095-3941.2021.0621

41. Perrone F, Zilbauer M. Biobanking of human gut organoids for translational research. *Exp Mol Med*. 2021;53(10):1451-1458.

doi: 10.1038/s12276-021-00606-x

42. Ravi K, Manoharan TJM, Wang KC, Pockaj B, Nikkhah M. Engineered 3D ex vivo models to recapitulate the complex stromal and immune interactions within the tumor microenvironment. *Biomaterials*. 2024;305:122428.

doi: 10.1016/j.biomaterials.2023.122428

43. Izadifar Z, Sontheimer-Phelps A, Lubamba BA, *et al*. Modeling mucus physiology and pathophysiology in human organs-on-chips. *Adv Drug Deliv Rev*. 2022;191:114542.

doi: 10.1016/j.addr.2022.114542

44. Li B, Tang Y, Huang Z, Ma L, Song J, Xue L. Synergistic innovation in organ-on-a-chip and organoid technologies: Reshaping the future of disease modeling, drug development and precision medicine. *Protein Cell*. Published online 2025.

doi: 10.1093/procel/pwaf058

45. Yang R, Qi Y, Zhang X, Gao H, Yu Y. Living biobank: Standardization of organoid construction and challenges. *Chin Med J*. 2024;137(24):3050-3060.

doi: 10.1097/CM9.0000000000003414

46. Miloradovic D, Pavlovic D, Jankovic MG, *et al*. Human Embryos, Induced Pluripotent Stem Cells, and Organoids: Models to Assess the Effects of Environmental Plastic Pollution. *Front Cell Dev Biol*. 2021;9.

doi: 10.3389/fcell.2021.709183

47. Li H, Liu S, Zhang J, Zhang C. Research progress of organoids derived from normal tissues. *Dig Med Res*. 2019;2:39.

doi: 10.21037/dmr.2019.12.04

48. Wang L, Ye Z, Jang YY. Convergence of human pluripotent stem cell, organoid, and genome editing technologies. *Exp Biol Med*. 2021;246(7):861-875.

doi: 10.1177/1535370220985808

49. Heinzelmann E, Piraino F, Costa M, *et al*. iPSC-derived and Patient-Derived Organoids: Applications and challenges in scalability and reproducibility as pre-clinical models. *Curr Res Toxicol*. 2024;7:100197.

doi: 10.1016/j.crtox.2024.100197

50. Liang Y, Sun X, Duan C, Tang S, Chen J. Application of patient-derived induced pluripotent stem cells and organoids in inherited retinal diseases. *Stem Cell Res Ther*. 2023;14(1).

doi: 10.1186/s13287-023-03564-5

51. Yan HHN, Chan AS, Lai FPL, Leung SY. Organoid cultures for cancer modeling. *Cell Stem Cell*. 2023;30(7):917-937.

doi: 10.1016/j.stem.2023.05.012

52. Xu Z, Yang J, Xin X, *et al*. Merits and challenges of iPSC-derived organoids for clinical applications. *Front Cell Dev Biol*. 2023;11.

doi: 10.3389/fcell.2023.1188905

53. Zhou G, Li R, Sheng S, *et al*. Organoids and organoid

extracellular vesicles-based disease treatment strategies. *J Nanobiotechnol*. 2024;22(1).

doi: 10.1186/s12951-024-02917-3

54. Lee H, Im JS, Choi DB, Woo DH. Trends in the global organoid technology and industry: from organogenesis in a dish to the commercialization of organoids. *Organoid*. 2021;1:e11.

doi: 10.51335/organoid.2021.1.e11

55. Mulaudzi PE, Abrahamse H, Crous A. Insights on Three Dimensional Organoid Studies for Stem Cell Therapy in Regenerative Medicine. *Stem Cell Rev Rep*. 2023;20(2):509-523.

doi: 10.1007/s12015-023-10655-6

56. Sean G, Banes AJ, Gangaraju R. Organoids and tissue/organ chips. *Stem Cell Res Ther*. 2024;15(1).

doi: 10.1186/s13287-024-03859-1

57. Goldrick C, Guri I, Herrera-Oropeza G, *et al*. 3D multicellular systems in disease modelling: From organoids to organ-on-chip. *Front Cell Dev Biol*. 2023;11.

doi: 10.3389/fcell.2023.1083175

58. Velasco V, Shariati SA, Esfandyarpour R. Microtechnology-based methods for organoid models. *Microsyst Nanoeng*. 2020;6(1).

doi: 10.1038/s41378-020-00185-3

59. Lai W, Geliang H, Bin X, Wang W. Effects of hydrogel stiffness and viscoelasticity on organoid culture: a comprehensive review. *Mol Med*. 2025;31(1).

doi: 10.1186/s10020-025-01131-7

60. Chen S, Schoen J. Air-liquid interface cell culture: From airway epithelium to the female reproductive tract. *Reprod Domestic Animals*. 2019;54(S3):38-45.

doi: 10.1111/rda.13481

61. Abo KM, Sainz de Aja J, Lindstrom-Vautrin J, *et al*. Air-liquid interface culture promotes maturation and allows environmental exposure of pluripotent stem cell-derived alveolar epithelium. *JCI Insight*. 2022;7(6).

doi: 10.1172/jci.insight.155589

62. Lamers MM, van der Vaart J, Knoops K, *et al*. An organoid-derived bronchioalveolar model for SARS-CoV-2 infection of human alveolar type II-like cells. *EMBO J*. 2021;40(5).

doi: 10.15252/embj.2020105912

63. Kim J, Eo EY, Kim B, *et al*. Transcriptomic Analysis of Air-Liquid Interface Culture in Human Lung Organoids Reveals Regulators of Epithelial Differentiation. *Cells*. 2024;13(23):1991.

doi: 10.3390/cells13231991

64. Rezaei Kolahchi A, Khadem Mohtaram N, Pezeshgi Modarres H, *et al*. Microfluidic-Based Multi-Organ Platforms for Drug Discovery. *Micromachines*. 2016;7(9):162.

doi: 10.3390/mi7090162

65. Mu P, Zhou S, Lv T, *et al*. Newly developed 3D in vitro models to study tumor-immune interaction. *J Exp Clin Cancer Res*. 2023;42(1).

doi: 10.1186/s13046-023-02653-w

66. Liu H, Gan Z, Qin X, Wang Y, Qin J. Advances in Microfluidic Technologies in Organoid Research. *Adv Healthc Mater*. 2023;13(21).

doi: 10.1002/adhm.202302686

67. Licata JP, Schwab KH, Har-el Y el, Gerstenhaber JA, Lelkes PI. Bioreactor Technologies for Enhanced Organoid Culture. *Int J Mol Sci*. 2023;24(14):11427.

doi: 10.3390/ijms241411427

68. Mousavi Shaegh SA, De Ferrari F, Zhang YS, *et al*. A microfluidic optical platform for real-time monitoring of pH and oxygen in microfluidic bioreactors and organ-on-chip devices. *Biomicrofluidics*. 2016;10(4).

doi: 10.1063/1.4955155

69. Chen VC, Couture LA. The suspension culture of undifferentiated human pluripotent stem cells using spinner flasks. In: *Methods in Molecular Biology*. Springer New York; 2014:13-21. doi:10.1007/7651_2014_118

70. Wiedenmann S, Breunig M, Merkle J, *et al*. Single-cell-resolved differentiation of human induced pluripotent stem cells into pancreatic duct-like organoids on a microwell chip. *Nat Biomed Eng*. 2021;5(8):897-913.

doi: 10.1038/s41551-021-00757-2

71. Sockell A, Wong W, Longwell S, *et al*. A microwell platform for high-throughput longitudinal phenotyping and selective retrieval of organoids. *Cell Syst*. 2023;14(9):764-776.e6.

doi: 10.1016/j.cels.2023.08.002

72. Zhang J, Xue J, Luo N, Chen F, Chen B, Zhao Y. Microwell array chip-based single-cell analysis. *Lab Chip*. 2023;23(5):1066-1079.

doi: 10.1039/D2LC00667G

73. Li Z, Yue M, Liu Y, *et al*. Advances of Engineered Hydrogel Organoids within the Stem Cell Field: A Systematic Review. *Gels*. 2022;8(6):379.

doi: 10.3390/gels8060379

74. Kaur S, Kaur I, Rawal P, Tripathi DM, Vasudevan A. Non-matrigel scaffolds for organoid cultures. *Cancer Letters*. 2021;504:58-66.

doi: 10.1016/j.canlet.2021.01.025

75. Phelan MA, Lelkes PI, Swaroop A. Mini and customized low-cost bioreactors for optimized high-throughput generation of tissue organoids. *Stem Cell Investig*. 2018;5:33.

doi: 10.21037/sci.2018.09.06

76. Zheng F, Xiao Y, Liu H, Fan Y, Dao M. Patient-Specific Organoid and Organ-on-a-Chip: 3D Cell-Culture Meets 3D

Printing and Numerical Simulation. *Adv Biol*. 2021;5(6).

doi: 10.1002/adbi.202000024

77. Price S, Bhosle S, Gonçalves E, *et al*. A suspension technique for efficient large-scale cancer organoid culturing and perturbation screens. *Sci Rep*. 2022;12(1).

doi: 10.1038/s41598-022-09508-y

78. Wang Y, Xue Y, Wang H, *et al*. Automated laser-assisted single-cell sorting for cell functional and RNA sequencing. *ACS Sens*. 2025;10(2):846-856.

doi: 10.1021/acssensors.4c02417

79. Papp D, Korcsmaros T, Hautefort I. Revolutionizing immune research with organoid-based co-culture and chip systems. *Clin Exp Immunol*. 2024;218(1):40-54.

doi: 10.1093/cei/uxae004

80. Zhao Z, Chen X, Dowbaj AM, *et al*. Organoids. *Nat Rev Methods Primer*. 2022;2(1).

doi: 10.1038/s43586-022-00174-y

81. Rabata A, Fedr R, Soucek K, Hampl A, Koledova Z. 3D Cell Culture Models Demonstrate a Role for FGF and WNT Signaling in Regulation of Lung Epithelial Cell Fate and Morphogenesis. *Front Cell Dev Biol*. 2020;8.

doi: 10.3389/fcell.2020.00574

82. Gu Z, Wu Q, Shang B, Zhang K, Zhang W. Organoid co-culture models of the tumor microenvironment promote precision medicine. *Cancer Innov*. 2024;3(1).

doi: 10.1002/cai2.101

83. Yang L, Wang X, Zhou X, *et al*. A tunable human intestinal organoid system achieves controlled balance between self-renewal and differentiation. *Nat Commun*. 2025;16(1).

doi: 10.1038/s41467-024-55567-2

84. Sun S, Xue X, Fu J. Modeling development using microfluidics: Bridging gaps to foster fundamental and translational research. *Curr Opin Genet Dev*. 2023;82:102097.

doi: 10.1016/j.gde.2023.102097

85. Yang H, Wang Y, Wang P, Zhang N, Wang P. Tumor organoids for cancer research and personalized medicine. *Cancer Biol Med*. 2021;18.

doi: 10.20892/j.issn.2095-3941.2021.0335

86. Sinha A, Maibam M, Jain R, *et al*. Organoid: Biomedical application, biobanking, and pathways to translation. *Heliyon*. 2025;11(10):e43028.

doi: 10.1016/j.heliyon.2025.e43028

87. Li Y, Tang P, Cai S, Peng J, Hua G. Organoid based personalized medicine: from bench to bedside. *Cell Regen*. 2020;9(1).

doi: 10.1186/s13619-020-00059-z

88. Huang Y, Huang Z, Tang Z, *et al*. Research Progress, Challenges, and Breakthroughs of Organoids as Disease Models. *Front Cell Dev Biol*. 2021;9.

doi: 10.3389/fcell.2021.740574

89. Hu Y, Sui X, Song F, *et al*. Lung cancer organoids analyzed on microwell arrays predict drug responses of patients within a week. *Nat Commun*. 2021;12(1).

doi: 10.1038/s41467-021-22676-1

90. Kretzschmar K. Cancer research using organoid technology. *J Mol Med*. 2020;99(4):501-515.

doi: 10.1007/s00109-020-01990-z

91. Heydari Z, Devasahayam Arokia Balaya R, Sarkar G, Boardman L. The Role of Organoids in Advancing Colorectal Cancer Research: Insights and Future Directions. *Cancers*. 2025;17(13):2129.

doi: 10.3390/cancers17132129

92. Maule G, Casini A, Montagna C, *et al*. Allele specific repair of splicing mutations in cystic fibrosis through AsCas12a genome editing. *Nat Commun*. 2019;10(1).

doi: 10.1038/s41467-019-11454-9

93. de Jongh D, Massey EK, Berishvili E, *et al*. Organoids: a systematic review of ethical issues. *Stem Cell Res Ther*. 2022;13(1).

doi: 10.1186/s13287-022-02950-9

94. Means JC, Martinez-Bengochea AL, Louiselle DA, *et al*. Rapid and scalable personalized ASO screening in patient-derived organoids. *Nature*. 2025;638(8049):237-243.

doi: 10.1038/s41586-024-08462-1

95. Ryu JO, Seong YJ, Lee E, Lee SY, Lee DW. Applications and research trends in organoid based infectious disease models. *Sci Rep*. 2025;15(1).

doi: 10.1038/s41598-025-07816-7

96. Peng L, Gao L, Wu X, *et al*. Lung organoids as model to study SARS-CoV-2 infection. *Cells*. 2022;11(17):2758.

doi: 10.3390/cells11172758

97. Sugimoto S, Kobayashi E, Fujii M, *et al*. An organoid-based organ-repurposing approach to treat short bowel syndrome. *Nature*. 2021;592(7852):99-104.

doi: 10.1038/s41586-021-03247-2

98. Zhang FL, Hu Z, Wang YF, *et al*. Organoids transplantation attenuates intestinal ischemia/reperfusion injury in mice through L-malic acid-mediated M2 macrophage polarization. *Nat Commun*. 2023;14(1).

doi: 10.1038/s41467-023-42502-0

99. Tan S, Ding Y, Wang W, *et al*. Development of an AI model for DILI-level prediction using liver organoid brightfield images. *Commun Biol*. 2025;8(1).

doi: 10.1038/s42003-025-08205-6

100. Forsythe SD, Devarasetty M, Shupe T, *et al*. Environmental Toxin Screening Using Human-Derived 3D Bioengineered

Liver and Cardiac Organoids. *Front Public Health*. 2018;6.

doi: 10.3389/fpubh.2018.00103

101. Zhou C, Wu Y, Wang Z, *et al*. Standardization of organoid culture in cancer research. *Cancer Med*. 2023;12(13):14375-14386.

doi: 10.1002/cam4.5943

102. Moon HR, Mun SJ, Kim TH, *et al*. Guidelines for Manufacturing and Application of Organoids: Liver. *Int J Stem Cells*. 2024;17(2):120-129.

doi: 10.15283/ijsc24044

103. Ahn SJ, Lee S, Kwon D, *et al*. Essential Guidelines for Manufacturing and Application of Organoids. *Int J Stem Cells*. 2024;17(2):102-112.

doi: 10.15283/ijsc24047

104. Xiang D, He A, Zhou R, *et al*. Building consensus on the application of organoid-based drug sensitivity testing in cancer precision medicine and drug development. *Theranostics*. 2024;14(8):3300-3316.

doi: 10.7150/thno.96027

105. Foo MA, You M, Chan SL, *et al*. Clinical translation of patient-derived tumour organoids- bottlenecks and strategies. *Biomark Res*. 2022;10(1).

doi: 10.1186/s40364-022-00356-6

106. Rogulska O, Havelkova J, Petrenko Y. Cryopreservation of organoids. *Cryo Letters*. 2023;44(2):65-75.

doi:10.54680/fr23210110112

107. Han H, Zhan T, Guo N, Cui M, Xu Y. Cryopreservation of organoids: Strategies, innovation, and future prospects. *Biotechnol J*. 2024;19(2).

doi: 10.1002/biot.202300543

108. Aarattuthodi S, Kang D, Gupta SK, *et al*. Cryopreservation of biological materials: applications and economic perspectives. *In Vitro CellDevBiol-Animal*. 2025;62(3):268-291.

doi: 10.1007/s11626-025-01027-0

109. Suarez-Martinez E, Suazo-Sanchez I, Celis-Romero M, Carnero A. 3D and organoid culture in research: physiology, hereditary genetic diseases and cancer. *Cell Biosci*. 2022;12(1).

doi: 10.1186/s13578-022-00775-w

110. Tok OE, Demirel G, Saatci Y, *et al*. Culturing, Freezing, Processing, and Imaging of Entire Organoids and Spheroids While Still in a Hydrogel. *J Vis Exp JoVE*. 2022;(190).

doi: 10.3791/64563

111. Gao Q, Wu Y, Mao Y, Chen X, Geng Z, Su J. Organoids: A new frontier in precision medicine and engineering. *Precis Med Eng*. 2025;2(4):100049.

doi: 10.1016/j.preme.2025.100049

112. Haake J, Steenpass L. Chromosomal quality control in hPSCs: A practical guide to SNP array analysis with GenomeStudio. *Front Cell Dev Biol*. 2025;13.

doi: 10.3389/fcell.2025.1599923

113. Huang W, Xu Z, Li S, Zhou J, Zhao B. Living Biobanks of Organoids: Valuable Resource for Translational Research. *Biopreservation Biobanking*. 2024;22(6):543-549.

doi: 10.1089/bio.2023.0142

114. Dagher G, Becker KF, Bonin S, *et al*. Pre-analytical processes in medical diagnostics: New regulatory requirements and standards. *New Biotechnol*. 2019;52:121-125.

doi: 10.1016/j.nbt.2019.05.002

115. Park JW, Bae SJ, Yun JH, Kim S, Park M. Assessment of Genetic Stability in Human Induced Pluripotent Stem Cell-Derived Cardiomyocytes by Using Droplet Digital PCR. *Int J Mol Sci*. 2024;25(2):1101.

doi: 10.3390/ijms25021101

116. Mead BE, Ordovas-Montanes J, Braun AP, *et al*. Harnessing single-cell genomics to improve the physiological fidelity of organoid-derived cell types. *BMC Biol*. 2018;16(1).

doi: 10.1186/s12915-018-0527-2

117. Shi X, Li Y, Yuan Q, *et al*. Integrated profiling of human pancreatic cancer organoids reveals chromatin accessibility features associated with drug sensitivity. *Nat Commun*. 2022;13(1).

doi: 10.1038/s41467-022-29857-6

118. Tindle C, Fonseca AG, Taheri S, *et al*. A living organoid biobank of patients with Crohn's disease reveals molecular subtypes for personalized therapeutics. *Cell Rep Med*. 2024;5(10):101748.

doi: 10.1016/j.xcrm.2024.101748

119. Dennison TW, Edgar RD, Payne F, *et al*. Patient-derived organoid biobank identifies epigenetic dysregulation of intestinal epithelial MHC-I as a novel mechanism in severe Crohn's Disease. *Gut*. 2024;73(9):1464-1477.

doi: 10.1136/gutjnl-2024-332043

120. Jiao C, Karakaya OF, Dadgar N, *et al*. Mastering Organoid Growth: A Complete Guide to Overcoming Methodological Challenges. *MedComm*. 2026;7(1).

doi: 10.1002/mco2.70571

121. Hansen SL, Larsen HL, Pikkupeura LM, *et al*. An organoid-based CRISPR-Cas9 screen for regulators of intestinal epithelial maturation and cell fate. *Sci Adv*. 2023;9(28).

doi: 10.1126/sciadv.adg4055

122. Ahammed B, Kalangi SK. A Decade of Organoid Research: Progress and Challenges in the Field of Organoid Technology. *ACS Omega*. 2024;9(28):30087-30096.

doi: 10.1021/acsomega.4c03683

123. Zhou Z, Cong L, Cong X. Patient-Derived Organoids in Precision Medicine: Drug Screening, Organoid-on-a-Chip and Living Organoid Biobank. *Front Oncol*. 2021;11.

doi: 10.3389/fonc.2021.762184

124. Alkhatib R, Gaede KI. Data Management in Biobanking: Strategies, Challenges, and Future Directions. *BioTech*. 2024;13(3):34.

doi: 10.3390/biotech13030034

125. Dove ES. Biobanks, Data Sharing, and the Drive for a Global Privacy Governance Framework. *J Law Med Ethics*. 2015;43(4):675-689.

doi: 10.1111/jlme.12311

126. Gross M, Dewan A, Macis M, *et al*. Decentralized biobanking platform for organoid research networks. *Front Blockchain*. 2025;8.

doi: 10.3389/fbloc.2025.1510429

127. Antoniades A, Papaioannou M, Malatras A, *et al*. Integration of Biobanks in National eHealth Ecosystems Facilitating Long-Term Longitudinal Clinical-Omics Studies and Citizens' Engagement in Research Through eHealthBioR. *Front Digit Health*. 2021;3.

doi: 10.3389/fdgth.2021.628646

128. Bai L, Zhou D, Li G, Liu J, Chen X, Su J. Engineering bone/cartilage organoids: strategy, progress, and application. *Bone Res*. 2024;12(1).

doi: 10.1038/s41413-024-00376-y

129. Grebenyuk S, Ranga A. Engineering Organoid Vascularization. *Front Bioeng Biotechnol*. 2019;7.

doi: 10.3389/fbioe.2019.00039

130. Zhou LF, Liao HY, Han Y, Zhao Y. The use of organoids in creating immune microenvironments and treating gynecological tumors. *J Transl Med*. 2024;22(1).

doi: 10.1186/s12967-024-05649-y

131. Lewis J, Holm S. Organoid biobanking, autonomy and the limits of consent. *Bioethics*. 2022;36(7):742-756.

doi: 10.1111/bioe.13047

132. Mollaki V. Ethical Challenges in Organoid Use. *BioTech*. 2021;10(3):12.

doi: 10.3390/biotech10030012