Cell Organoid

Review

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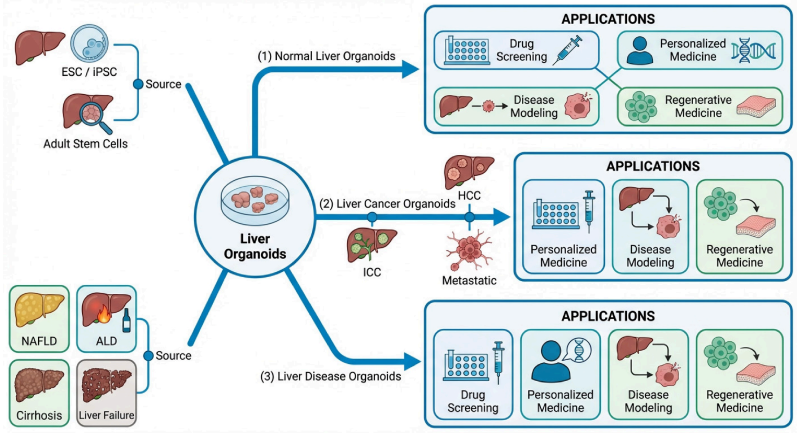
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In Brief

This review compares normal, cancer, and other liver disease organoids by cell source, cellular complexity, microenvironment, maturation, and intended use. It evaluates adult hepatocyte, multicellular, vascularized, and zonated systems for disease modeling and drug testing, while distinguishing established research applications from investigational precision oncology, transplantation, and bioartificial liver support.

Graphical abstract



Highlights

- Cell source, complexity, niche, maturation, and intended use guide model selection.
- Multicellular, vascularized, and zonated organoids improve functional modeling.
- Cancer and disease organoids support mechanistic studies and drug screening.
- Precision oncology, transplantation, and liver support remain investigational.

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Landscape of liver organoids, liver cancer organoids, and other liver disease organoids

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ABSTRACT

The liver is the body's central metabolic organ. Liver organoids have emerged as powerful tools to model it. Three-dimensional organoid systems are expected to reproduce many key liver functions. These functions include detoxification, protein synthesis, and bile production. Liver organoids allow researchers to study liver biology, disease mechanisms, and drug responses in vitro. This review systematically examines liver organoid development. We cover classification, cellular origins, cellular complexity, microenvironment composition, maturation state, translational status, culture methods, and applications. We detail several organoid types. Some derive from embryonic stem cells, induced pluripotent stem cells, or adult stem cells. Others are derived from patients' tumor tissues and tumor-related samples for liver cancer organoid generation. These include hepatocellular carcinoma organoids, intrahepatic cholangiocarcinoma organoids, and metastatic lesion organoids. We also discuss other disease-specific organoids. These model metabolic dysfunction-associated steatotic liver disease (MASLD), cirrhosis, viral hepatitis, and autoimmune disorders. The review explores key applications. These include basic research, drug discovery, toxicology testing, and regenerative medicine. We also consider future directions, such as bioartificial liver systems. By synthesizing recent advances, this work provides a comprehensive reference. It shows how liver organoids are advancing liver disease research and translational applications.

KEYWORDS

liver organoids, metabolism model, cancer organoids, disease modeling, precision medicine, regenerative medicine, bioartificial liver

1 Introduction

The liver, our largest internal organ, executes over 500 essential functions, from metabolism and detoxification to protein synthesis—yet globally, liver diseases account for nearly two million deaths annually, driven largely by cirrhosis, hepatocellular carcinoma (HCC), and viral hepatitis[1,2]. HCC alone ranks as the sixth most common cancer worldwide and stands as the third leading cause of cancer-related mortality[2]. Confronted with such a severe public health burden, there is an urgent need for more accurate disease models and innovative therapeutic approaches.

Traditional two-dimensional cell cultures lack the spatial architecture and cellular interplay of real liver tissue, while animal models are limited by species divergence, expense, and ethical issues[3,4]. In response, organoid technology has risen as a promising alternative. These three-dimensional, self-organizing structures derived from stem cells mimic key aspects of organ physiology *in vitro*[5]. Since the landmark 2009 work by Hans Clevers' lab, which generated intestinal organoids from a single Lgr5+ stem cell, the field has expanded rapidly to include liver, pancreas, brain, and many other tissue types[3,5–7].

Liver organoids, in particular, have evolved from basic experimental tools into important tools for modeling diseases, screening drugs, and advancing regenerative strategies[8]. This review synthesizes current progress across normal, cancerous, and diseased liver organoids—covering their origins, classification, species variations, methodological advances, and translational applications. By examining both achievements and ongoing

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challenges, we outline how these models may contribute to the future of liver disease research and clinical care.

1.1 Literature search strategy

This article is a narrative review. Literature was identified through searches of PubMed, Web of Science Core Collection, and Scopus for English-language studies published from January 2009 to June 2026. Search terms included combinations of "liver organoid", "hepatic organoid", "liver cancer organoid", "patient-derived organoid, "MASLD, "MASH, "fibrosis, "viral hepatitis", "organoid-on-chip, and "bioartificial liver. Reference lists of key primary studies and recent reviews were also screened. Priority was given to liver-specific primary studies and recent methodological or translational reports. No formal meta-analysis or risk-of-bias assessment was performed.

2 Definitions and classification

Organoids are three-dimensional structures that self-assemble from stem or progenitor cells in culture, offering greater physiological relevance than traditional two-dimensional systems[5]. Their defining characteristics include tissue-like spatial organization, cellular diversity encompassing both mature and progenitor cells, self-renewal capability, and retention of donor-specific genetic and phenotypic traits[9]. Liver organoids extend these principles to create *in vitro* models that replicate key structural and functional aspects of hepatic tissue[10].

These models can be classified by their cellular origins. Pluripotent stem cell-derived organoids emerge through differentiation protocols that guide cells toward hepatocyte and cholangiocyte lineages[6,11]. Adult stem cell-based systems typically originate from EpCAM+ or Lgr5+ hepatic progenitors, with established protocols now spanning both murine and human applications[3,10]. Patient-derived organoids maintain the unique genetic profile of individual donors when cultured directly from clinical samples[12].

From a translational perspective, liver organoids serve distinct purposes. Normal hepatic organoids facilitate studies of liver development and regeneration[13]. Cancer models represent various malignancies, including hepatocellular carcinoma, cholangiocarcinoma, and metastatic tumors[14,15]. Disease-specific organoids encompass conditions ranging from metabolic disorders and fibrosis to viral infections, autoimmune diseases, and genetic liver conditions[16–19]. This systematic categorization enables targeted modeling of hepatic physiology and pathology.

2.1 Cell tracing and general classification of normal liver and liver disease organoids

The fundamental logic of liver organoid construction lies in using cells to "trace" their *in vivo* identity. Based on essential differences in cell sources and the complexity of the microenvironment simulated *in vitro*, normal and diseased liver organoids can be clearly divided into two major technical pathways and maturity lineages.

I. Classification by cell source

Pluripotent stem cell (PSC) sources: including embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs). These organoids are built by mimicking embryonic developmental directed differentiation processes (definitive endoderm → hepatic bud → hepatocytes/cholangiocytes). Their main advantages include unlimited expandability and the ability to generate multi-lineage co-differentiation models, including hepatocytes, stellate cells, endothelial cells, and Kupffer cells, thereby more faithfully reconstructing the human liver microenvironment[20,21]. Recent advances even allow simulation of fetal liver hematopoiesis, simultaneously producing functional myeloid cells (e.g., macrophages, neutrophils) with immune functions[22].

Adult stem cell (ASC) sources: Primarily from liver tissue (especially Lgr5+ epithelial progenitors around bile ducts) or primary hepatocytes/cholangiocytes. These organoids rely on growth factor combinations that mimic the adult tissue "repair niche" (e.g., R-spondin1, EGF, FGF). Their core advantages include high genetic stability, rapid expansion efficiency, and direct preservation of patient tissue pathological features, making them the preferred choice for establishing disease models (e.g., hereditary liver diseases, primary sclerosing cholangitis)[10,13].

Other sources: Include induced liver stem cells directly transdifferentiated from fibroblasts, and patient-derived organoids (PDOs) established directly from tumor tissue or biopsy specimens[12,14].

II. Grading by microenvironment complexity and cellular composition

Based on the diversity of included cell lineages, liver organoids can be divided into several tiers:

Mono-/bi-lineage basic models: Composed mainly of hepatocytes or biliary epithelial cells. Although structurally simple, they enable efficient expansion and are suitable for large-scale drug screening and gene editing studies[13,23].

Multi-lineage complex models: This is the technological frontier in recent years. The construction of five-cell-lineage liver organoids (integrating hepatocytes, cholangiocytes, hepatic stellate cells, endothelial cells, and Kupffer cells) marks that *in vitro* platforms can "simulate" liver intercellular communication. Particularly when stellate cells are introduced, models can identify "indirect hepatotoxicity" dependent on non-parenchymal cell mediation (e.g.), drug-induced exosomal damage mechanisms), which traditional single-cell models cannot achieve[24].

Compartmentalized/vascularized models: The latest cutting-edge models achieve metabolic zonation (Zone 1/2/3). By co-culturing vascular endothelial cells or applying fluid shear force in microfluidic chips, the maturity and drug metabolism prediction capability of organoids are significantly enhanced[21,25].

Ⅲ. Current status by differentiation maturity and function

Immature/fetal status: Currently, most PSC-derived organoids are transcriptionally closer to fetal-stage liver, with lower expression levels of metabolic enzymes (e.g., CYP450)[26].

Trending toward maturity: By constructing vascularized structures in microfluidic chips or simulating physiological fluid flow, or utilizing zone-specific induction (e.g., ascorbate-mediated regionalized differentiation), organoids can be driven toward adult mature status, manifested by increased albumin secretion and establishment of urea cycle capacity[21,27].

Summary: From a practical perspective, adult stem cell- or tissue-derived organoids are particularly useful for preserving donor-specific epithelial phenotypes and modeling epithelial disorders and liver cancer, whereas PSC-derived multi-lineage organoids are better suited to studying processes that depend on interactions among parenchymal, stromal, vascular, and immune cell populations, such as steatohepatitis and complex hepatotoxicity[28,29]. A major limitation of many PSC-derived liver organoids is their incomplete maturation and fetal-like phenotype. Recent advances in multicellular co-differentiation,

vascularization, and organoid-on-chip technologies are helping to improve cellular complexity and functional maturation, although fully adult-like liver function has not yet been consistently achieved[18,30].

2.2 Integrated classification matrix

To complement the descriptive classification above, Table 1 summarizes liver organoid models across five practical dimensions requested for model selection: cell source, cellular complexity, microenvironmental composition, maturation state, and translational application.

3 Species-specific characteristics of liver organoid models

Liver organoids exhibit substantial species-dependent variation in culture parameters, biological functions, and translational applicability (Fig. 1). Recognizing these differences proves essential for selecting suitable models and interpreting experimental outcomes[31]. Human liver organoids, established from bipotent hepatic stem cells, demonstrate long-term genomic stability and offer the most direct physiological relevance for clinical translation[10]. Their advantages encompass direct representation of human hepatic biology, applicability in precision medicine and drug response testing, and maintenance of human-specific cytochrome P450 enzymatic profiles (approximately functional CYP genes[27])[32]. The relative scarcity and surgical origin of human hepatic tissue, however, impose notable constraints on their establishment.

In contrast, mouse liver organoids derived from Lgr5-positive progenitor cells can be robustly established and expanded using well-characterized culture protocols, making them useful for mechanistic studies, genetic manipulation, and investigations of liver regeneration[3,33]. However, substantial species differences in drug-metabolizing enzymes, particularly the cytochrome P450 system, limit direct extrapolation of murine data to human drug metabolism. Several major CYP gene clusters are considerably expanded in mice compared with humans[34]. A well-known example of such species-specific toxicity is fialuridine (FIAU), whose severe hepatotoxicity in human clinical trials was not predicted by conventional preclinical studies in mice, rats, dogs, or non-human primates[35].

Rat organoids require modulated Wnt activation and BMP inhibition, developing cystic structures with high Lgr5 expression[31]. Their established role in pharmacological research makes them valuable for traditional drug metabolism and toxicity assessment. For preclinical translation, non-human primate organoids—particularly from cynomolgus monkeys—exhibit the closest similarity to human systems in drug metabolism prediction[36]. These models demonstrate enhanced capability in

Table 1. Integrated classification matrix for liver organoid models.

Dimension	Main categories	Typical strengths	Key limitations
Cell source	PSC; adult tissue/primary cells; patient-derived tissue	Developmental modeling; donor-specific biology; tumor heterogeneity	Source-dependent maturation, access, and establishment efficiency
Cellular complexity	Mono-/bi-lineage; multicellular; assembloid	Cell–cell crosstalk; inflammation; fibrosis; immunotherapy	Higher variability, cost, and analytical complexity
Microenvironment	ECM-supported; tissue-fragment; vascularized; organoid-on-chip	Spatial organization; perfusion; zonation; niche interactions	Platform-specific artifacts and lower throughput
Maturation state	Fetal-like/intermediate; adult-like	Adult metabolism; DILI; transplantation-oriented studies	Many PSC-derived models remain incompletely mature
Translational application	Mechanistic studies; screening; precision oncology; regenerative research	Fit-for-purpose model selection and evidence interpretation	No single organoid format is optimal for all applications

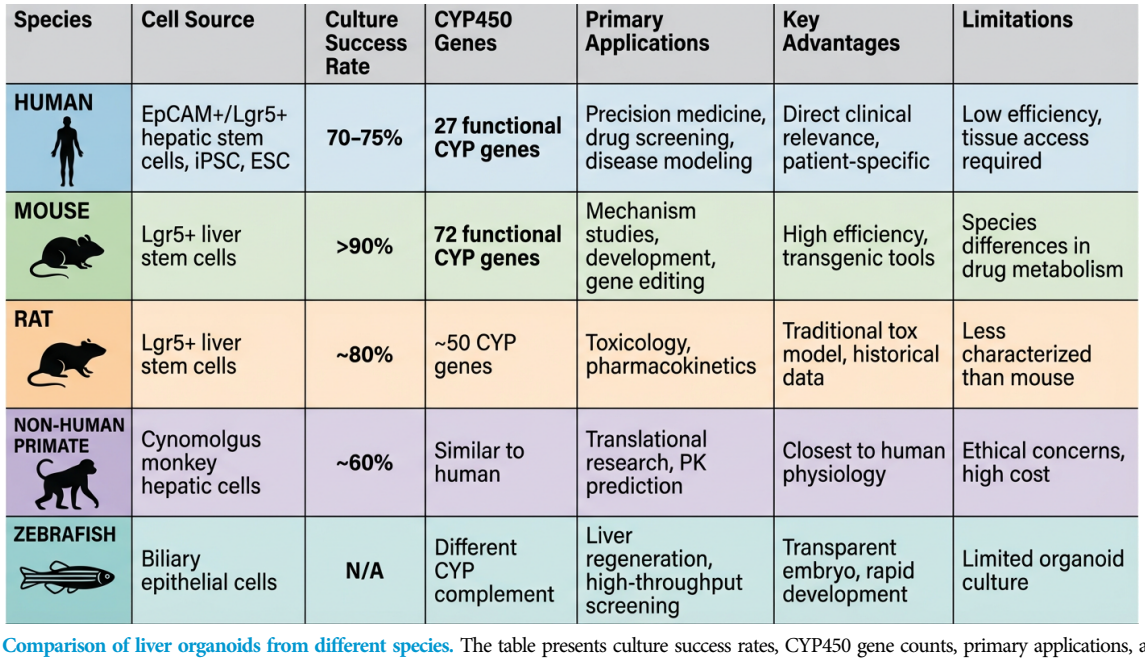


Figure 1. Comparison of liver organoids from different species. The table presents culture success rates, CYP450 gene counts, primary applications, advantages, and limitations of human, mouse, rat, non-human primate, and zebrafish liver organoids.

forecasting human pharmacokinetic parameters during drug development.

While zebrafish models employ different methodologies from conventional organoid systems, their optical transparency, genetic accessibility, and regenerative mechanisms involving biliary epithelial cells contribute valuable insights to liver research[37]. The complementary strengths across these model systems collectively enhance our capacity to investigate hepatic biology and advance therapeutic development .

4 Development of human liver organoid research

The development of human liver organoids has advanced from foundational research to diverse applications, with key phases marking technological progress[30] (Fig. 2). The field originated with Sato and Hans Clevers' 2009 demonstration that single Lgr5-positive intestinal stem cells could form crypt-villus structures in Matrigel, establishing the self-organizing potential of adult stem cells and identifying essential culture factors[5,33]. In 2013, Huch et al. showed that mouse Lgr5-positive liver stem cells could expand and differentiate into functional hepatocytes under Wnt stimulation, while Takebe et al. generated vascularized liver buds from iPSCs, both demonstrating therapeutic potential[3,6].

Between 2014 and 2018, advances included long-term culture protocols for human hepatic stem cells and standardized methods for mouse and human organoid manipulation[10,33]. In 2017, primary liver cancer organoids were established for tumor heterogeneity studies, and organoids began modeling genetic liver diseases[14,38]. By 2018, cancer organoids could be generated from biopsy specimens, expanding patient access[12]. The period 2019–2022 saw organoid applications broaden to steatohepatitis modeling, liver regeneration studies, and disease modeling for fibrosis, viral hepatitis, and hereditary conditions[7,17,28,39,40].

Since 2023, research has emphasized clinical translation, with large-scale organoid biobanks enabling proteogenomic characterization[41,42]. Recent work has produced vascularized liver organoids through self-organizing sinusoidal vessel systems[25], and bioartificial liver systems have shown promising preclinical results, although clinical evaluation remains limited. A comprehensive 2025 review by the Clevers' group synthesized these developments and outlined future directions[30], highlighting the transition from experimental systems to translational platforms in liver organoid research.

The field has continued to advance rapidly in 2025–2026. Notable milestones include Igarashi and colleagues' establishment of the first expandable adult hepatocyte organoids with full metabolic functions, including CYP450 activity and drug metabolism capacity[20]. Al Reza et al. reported multi-zonal liver organoids from human pluripotent stem cells that replicate periportal, interzonal, and pericentral metabolic zones[21]. Saiki et al. demonstrated self-organization of functional sinusoidal vessels in PSC-derived liver bud organoids, achieving perfused vascular networks capable of producing coagulation factors[25]. Dowbaj et al. developed mouse liver assembloids modeling periportal architecture and biliary fibrosis through multi-cellular co-culture systems[43]. In 2026, Pohlberger et al. reported the establishment of 45 patient-derived organoid lines from healthy, steatotic, and cirrhotic tissues, providing a comprehensive platform for comparative disease modeling[44].

5 Sources and culture of normal liver organoids

Normal liver organoids can be established from multiple cell sources, each possessing unique advantages and optimal applications[3].

5.1 Embryonic stem cell-derived liver organoids

Embryonic stem cells (ESCs) serve as a foundational source for liver organoid generation due to their capacity for unlimited proliferation and differentiation into multiple lineages[17]. To direct ESC differentiation toward hepatic cell types, protocols typically recapitulate embryonic developmental stages—initiating with definitive endoderm induction, progressing through hepatic foregut specification, and culminating in the generation of hepatocytes and cholangiocytes. This differentiation process is guided by specific signaling molecules, including Activin A, BMP4, FGF2, and HGF. Demonstrating their translational

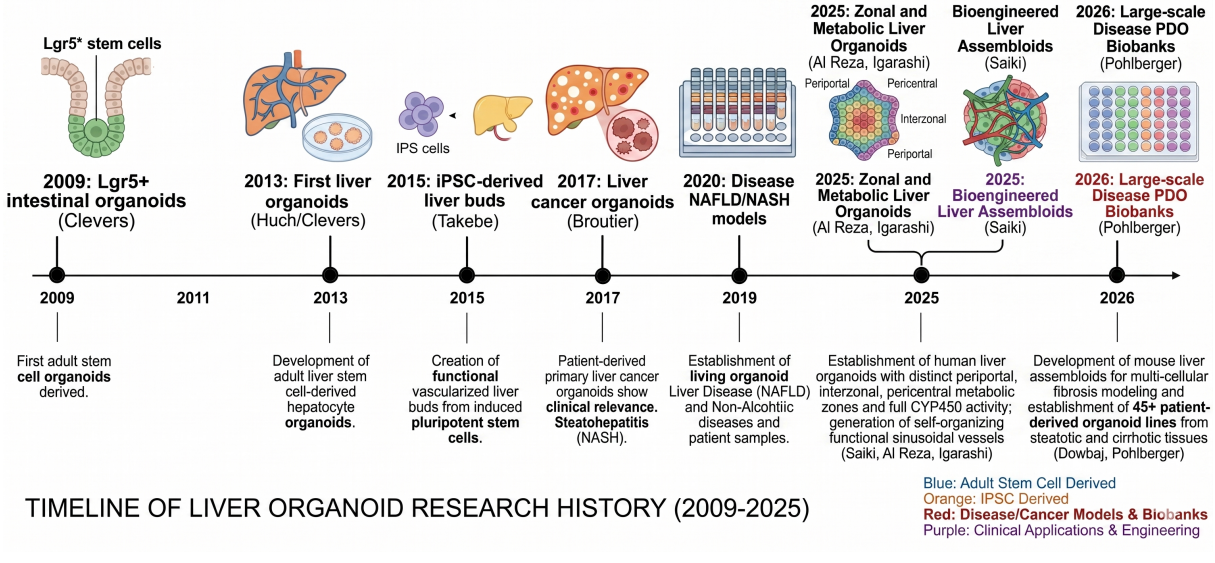


Figure 2. Timeline of key milestones in liver organoid research (2009–2026). From the breakthrough discovery of Lgr5-positive intestinal organoids in 2009 to vascularized liver organoids, multi-zonal systems, and bioartificial liver applications in 2025–2026, the timeline illustrates the pivotal milestones in the liver organoid field.

relevance, expandable hepatic organoids derived from human ESCs have shown significant promise for applications in liver regeneration research and disease modeling[17].

Recent advances have further enhanced the functional maturity of ESC/iPSC-derived organoids. Liu et al. developed expandable and mature hiPSC-derived liver organoids (SB-HEOs) using a SB431542/BMP4 hepatic endoderm protocol; these organoids exhibit high CYP450 drug metabolism activity confirmed by LC-MS/MS, accurately distinguish hepatotoxic from non-hepatotoxic drugs, and successfully repopulate FRG mouse livers[27]. These developments address a longstanding limitation of PSC-derived organoids—namely, their fetal-like metabolic profile—and bring them closer to adult hepatocyte functionality.

5.2 Induced pluripotent stem cell–derived liver organoids

Induced pluripotent stem cell (iPSC) technology bypasses the ethical concerns of ESCs by reprogramming a patient's own somatic cells—for example, skin fibroblasts or peripheral blood mononuclear cells—into pluripotent stem cells[6]. The resulting iPSC-derived liver organoids preserve the donor's unique genetic profile, which makes them especially valuable for modeling hereditary liver disorders and tailoring personalized therapeutic strategies.

Pioneering work from the Takebe group has significantly advanced this field. In 2013, they demonstrated the self-assembly of vascularized liver buds by co-culturing iPSC-derived hepatic endoderm cells with endothelial and mesenchymal stem cells[6]. By 2017, they had scaled this process to achieve high-yield, reproducible production of these structures[11]. Building on this progress, Mun et al. established an expandable hepatocyte-like liver organoid system from human pluripotent stem cells in 2019[26].

A major recent breakthrough is the development of multi-zonal liver organoids from human PSCs. Al Reza et al. created self-assembling zone-specific organoids by co-culturing ascorbate-enriched (zone 1-like) and bilirubin-enriched (zone 3-like) hepatic progenitors, producing organoids containing hepatocytes, cholangiocytes, endothelial cells, stellate cells, and macrophages that exhibit zone-specific toxicant responses[21]. This advance enables physiologically relevant modeling of zone-selective drug metabolism and hepatotoxicity.

5.3 Adult stem cell-derived liver organoids

Liver organoids developed from adult stem cells (ASCs) originate directly from liver tissue, preserving its characteristic epigenetic landscape[10,13]. These organoids commonly arise from two key progenitor populations: EpCAM-positive cells, which effectively generate organoid cultures[45], and Lgr5-positive cells that serve as Wnt-responsive hepatic stem cell markers[3,9]. Successful propagation of ASC-derived organoids relies on a defined growth factor cocktail containing EGF, HGF, R-spondin 1, FGF10, nicotinamide, and A83-01—the latter being a TGF-β inhibitor particularly essential for maintaining human cultures[33].

In 2025, Igarashi et al. achieved a major breakthrough by establishing expandable adult hepatocyte organoids from single ASGPR1+ EpCAM− human hepatocytes through combined Wnt and STAT3 activation[20]. These organoids demonstrate major liver metabolic functions comparable to *in vivo* hepatocytes, including albumin secretion, bile acid synthesis and conjugation, coagulation factor production, and rifampicin-inducible CYP3A activity. Upon niche factor removal and hormone supplementation, they form bile canalicular networks and exhibit clinically coherent acetaminophen injury responses. This system resolves the long-standing trade-off between expandability and functional competency in hepatocyte cultures.

5.4 Patient- and clinical tissue-derived liver organoids

Clinical tissue–derived liver organoids can be established using enzymatic dissociation or tissue-fragment/suspension approaches. Dissociation-based protocols facilitate standardized expansion and downstream screening, whereas tissue-fragment approaches may retain additional stromal, immune, or microvascular components (Fig. 3). Recent ICC studies illustrate these complementary

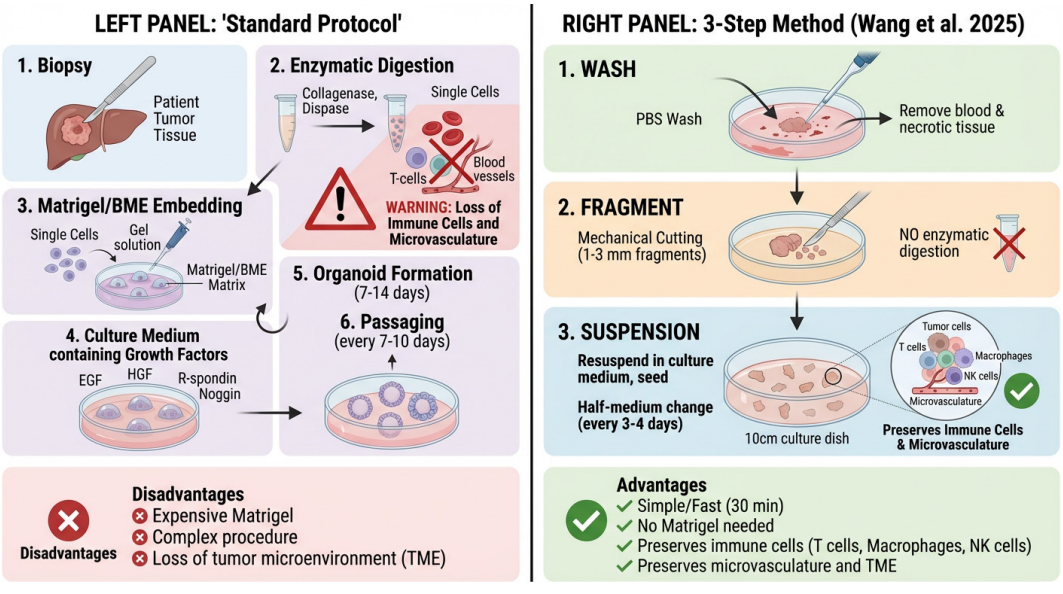


Figure 3. Comparative Evaluation of Liver Organoid Culture Protocols. Left– Standard Protocol: Clinical is enzymatically dissociated and embedded in extracellular matrix. This approach supports standardized expansion but may reduce retention of native microenvironmental components. Right–Three-step Method: Washed tissue is mechanically fragmented and maintained in suspension culture. This approach may preserve selected immune and microvascular components during early culture; the extent and duration of such preservation require independent validation.

strategies, but the degree and duration of microenvironment preservation vary among protocols and require independent validation.

Direct comparisons should therefore report establishment efficiency, cellular composition, genomic and phenotypic fidelity, and suitability for downstream assays rather than assuming the superiority of one culture approach. Standardization across centers and correlation with patient outcomes remain important priorities.

A notable development in 2026 was reported by Pohlberger et al., who established 45 patient-derived liver organoid lines from 207 liver surgeries with an 82% initiation success rate[44]. Their optimized protocol enables organoid initiation from healthy, steatotic (MASLD), and cirrhotic tissues, with quantitative modeling revealing biphasic growth dynamics and inter-patient heterogeneity in hepatocyte marker expression. This platform provides a physiologically relevant system for dissecting disease progression mechanisms across diverse patient cohorts.

5.5 Practical cost considerations

Because reagent prices, labor, tissue access, and instrument availability vary widely among institutions, fixed monetary estimates may be misleading. Table 2 therefore provides a relative research-scale cost profile for major liver organoid modules and highlights their principal cost drivers.

Actual costs vary substantially among laboratories because of differences in reagent suppliers, geographic regions, experimental scale, labor, and access to shared facilities; therefore, the table provides only a relative comparison rather than fixed monetary estimates

6 Liver cancer organoids

Liver cancer organoids provide a valuable platform for studying tumor heterogeneity, screening anticancer drugs, and developing personalized therapeutic strategies[14,46].

6.1 HCC organoids

Hepatocellular carcinoma (HCC) represents the predominant subtype of primary liver cancer, accounting for approximately 80% of cases worldwide[47]. HCC organoids can be established from surgical specimens or biopsy samples and have emerged as valuable models for investigating tumor heterogeneity, therapeutic responses, and personalized treatment strategies[42]. Early studies demonstrated that patient-derived HCC organoids could preserve key characteristics of parental tumors, including histological features, genomic alterations, and transcriptomic profiles, providing a reliable ex vivo platform for cancer biology studies[14].

Subsequent advances in organoid biobanking and multi-omics profiling have expanded their translational potential[12]. Large-scale HCC organoid collections, such as the Liver Cancer Organoid Biobank, have enabled molecular classification of tumor subtypes and identification of differential drug responses associated with specific genomic and proteomic signatures[41]. More recently, Yang et al. established a large patient-derived liver cancer organoid biobank and demonstrated that organoid drug responses could partially reflect clinical responses in relapsed patients, highlighting their potential utility for functional precision oncology[42]. However, prospective validation in larger cohorts is still required before HCC organoids can be routinely incorporated into clinical decision-making.

6.2 ICC organoids

Intrahepatic cholangiocarcinoma (ICC) accounts for 10%–15% of primary liver cancers and carries a particularly poor prognosis owing to late diagnosis and limited therapeutic options[2]. ICC organoids have been successfully generated from surgical specimens and biopsies, recapitulating the glandular architecture and mucin production characteristic of biliary tract malignancies[14]. Comparative molecular profiling of HCC and ICC organoids has revealed distinct lineage-specific dependencies, with ICC organoids exhibiting greater sensitivity to inhibitors of fibroblast growth factor receptor (FGFR) and isocitrate dehydrogenase 1 (IDH1), reflecting the genomic landscape of biliary malignancies[14]. Recent advances in 2025 have expanded the repertoire of ICC modeling approaches, with refined culture conditions enabling improved representation of the desmoplastic stroma and tumor microenvironment that characterizes this cancer type.

6.3 Liver metastasis organoids

Colorectal cancer liver metastasis (CRLM) represents the most common hepatic metastatic disease, and organoid models have proven instrumental in dissecting the molecular determinants of metastatic colonization. Kim et al. performed integrative multi-omics analysis of five matched primary-metastatic colorectal cancer organoid pairs, incorporating genetic, transcriptional, exosomal miRNA, and pharmacological profiling[48]. Machine learning integration of these multi-omics layers constructed a drug response prediction model that recapitulated druggable molecular targets specifically dysregulated in liver metastasis organoids and revealed statistical connections to systemic therapy regimens. Zhou et al. utilized patient-derived organoid modeling to identify USP3-AS1 as a novel promoter in CRLM through increasing glucose-driven histone lactylation[49]. Using five pairs of organoids from primary tumors and matched liver metastatic lesions, the authors demonstrated that USP3-AS1 was significantly upregulated in CRLM-derived organoids, enhancing sphere formation efficiency and metastatic potential. Mechanistic analysis revealed that USP3-AS1 stabilized MYC via post-translational deubiquitination, thereby promoting glycolysis and histone H3K18 lactylation, providing a metabolic axis relevant to therapeutic targeting[49].

Table 2. Relative cost and resource profile for major liver organoid modules.

Module	Main cost drivers	Relative resource requirement
Adult tissue-derived organoids	ECM, growth factors, routine culture	Moderate
PSC-derived organoids	PSC maintenance, staged differentiation factors, long culture period	High
Patient-derived tumor organoids	Clinical sample processing, ECM, genomic/QC assays	Moderate–high
Multicellular/immune organoids	Multiple cell types, cytokines, phenotyping	High
Organoid-on-chip/vascularized systems	Chips, perfusion equipment, endothelial cells, imaging	Very high

6.4 cHCC-CCA organoids

Combined hepatocellular-cholangiocarcinoma (cHCC-CCA) is a rare but clinically significant entity with features of both HCC and ICC. Organoid models of cHCC-CCA have been generated that maintain the biphenotypic differentiation characteristics of the parental tumors[14]. These models have proven particularly valuable for dissecting the clonal origins and lineage plasticity underlying mixed liver cancers, with transcriptomic and histopathological analyses supporting their faithful representation of the original tumor heterogeneity.

6.5 Hepatoblastoma organoids

Hepatoblastoma, the most common pediatric liver malignancy, has been modeled using organoid technology to recapitulate the fetal hepatic differentiation programs characteristic of this disease. Van Son et al. established a fully annotated hepatoblastoma tumoroid biobank comprising 14 tumoroid lines from 9 patients, providing a systematic resource for studying treatment-induced evolution and clonal dynamics in pediatric liver cancer[50]. This biobank enables longitudinal tracking of therapeutic responses and clonal selection pressures, offering insights into the developmental origins and therapeutic vulnerabilities of hepatoblastoma.

6.6 Drug screening and precision medicine

The application of liver cancer organoids to high-throughput drug screening and precision medicine has advanced considerably. The predictive value of organoid drug response profiling for patient stratification has been demonstrated across multiple cancer types, although direct concordance data specifically for liver cancer organoids remain more limited than for other gastrointestinal malignancies. Notably, the frequently cited 87% drug response concordance between organoids and patient outcomes was established in a gastric cancer study[51] and should not be extrapolated directly to liver cancer without liver-specific validation. In the liver cancer context, Yang et al. demonstrated that drug sensitivity or resistance observed in organoids corresponded to clinical responses in 14 relapsed patients, providing important liver-specific evidence for the translational relevance of organoid pharmacotyping[42]. Du et al. reviewed advances in organoid models for T cell-based immunotherapy in hepatobiliary cancers, highlighting the integration of organoid technology with chimeric antigen receptor T cell (CAR-T) therapy and immune checkpoint inhibition strategies for this challenging tumor type[52].

The clinical translation of organoid-based drug screening continues to expand. Hundreds of organoid-related clinical trials have been registered in oncology, although precise figures require verification against current registry databases owing to the rapid pace of trial initiation and completion. The integration of liver cancer organoids with pharmacogenomic profiling, as exemplified by the LICOB biobank[41] and the 399-organoid biobank[42], represents a promising avenue for functional precision medicine in primary liver cancer.

7 Liver disease organoids

7.1 Metabolic dysfunction-associated steatotic liver disease and MASH models

Metabolic dysfunction-associated steatotic liver disease (MASLD) and its progressive form, metabolic dysfunction-associated steatohepatitis (MASH), represent a leading cause of chronic liver disease worldwide[53]. Liver organoid models have emerged as valuable tools for recapitulating the spectrum of MASLD pathogenesis, from simple steatosis to steatohepatitis with inflammation and fibrosis. Ouchi et al. developed multicellular liver organoids from human pluripotent stem cells (PSCs) co-differentiated into hepatocyte-like, stellate-like, and Kupffer-like cells; treatment with free fatty acids induced steatosis, hepatocyte ballooning, inflammatory cytokine secretion (IL-6, IL-8, and TNF-α), and stellate cell activation with concomitant organoid stiffness increase, faithfully modeling the stepwise progression of steatohepatitis[28]. Gurevich et al. demonstrated that hepatocytes derived from NASH donors' iPSCs exhibited spontaneous lipid accumulation even without exogenous fatty acid supplementation, recapitulating intrinsic metabolic defects[54]. McCarron et al. generated organoids from liver cells of patients with NASH, which exhibited upregulation of metabolic and pro-inflammatory pathways and displayed all typical features of steatohepatitis, including reduced albumin secretion, increased apoptosis sensitivity, and lipid accumulation[55].

More recent advances in 2025–2026 have introduced refined multicellular models incorporating endothelial cells alongside hepatocytes, Kupffer cells, and stellate cells within liver-on-chip platforms. These models more closely reproduce selected pathological stages of MASLD/MASH progression, from steatosis through neovascularization, inflammation, and fibrosis, and may improve evaluation of stage-specific drug responses[56]. Goswami et al. demonstrated that liver organoids derived from hepatocytes of healthy individuals and patients with fatty liver disease displayed multilineage architecture with expression of nonparenchymal cell markers, including stellate cells (CD166) and Kupffer-like cells (CD68, EMR1), and developed steatohepatitis phenotypes responsive to metformin and saroglitazar[57]. Hendriks et al. established engineered human hepatocyte organoids enabling CRISPR-based target discovery and drug screening for steatosis, providing a genetically tractable platform for NAFLD mechanism investigation[58]. Igarashi et al. developed expandable human adult hepatocyte organoids that maintain adult hepatic identity and functions, including CYP activities and bile acid conjugation, enabling modeling of metabolic disease and drug-induced liver injury with adult-like metabolic fidelity[20].

7.2 Alcohol-associated liver disease models

Alcohol-associated liver disease (ALD) encompasses a spectrum from steatosis to alcohol-associated hepatitis, fibrosis, and cirrhosis. Wang et al. generated coculture liver organoids derived from embryonic stem cells with fetal liver mesenchymal cells; exposure to ethanol produced pathological features of alcohol-induced liver injury, including elevated CYP2E1 activity, oxidative stress, lipid accumulation, and fibrogenesis[17]. These models provide a useful experimental platform for investigating the pathogenesis of ALD and identifying potential therapeutic targets. Multicellular organoid systems incorporating Kupffer cells and stellate cells have further enhanced the representation of ethanol-induced inflammatory and fibrotic responses[28].

7.3 Hepatic fibrosis and cirrhosis models

Hepatic fibrosis and cirrhosis represent the common end-stage pathway of chronic liver diseases. Organoid models incorporating hepatic stellate cells (HSCs) have proven particularly valuable for studying fibrogenesis. In 2025, Mochida et al. established iPSC-

derived hepatocyte-stellate cell surrounding organoids (iHSOs), in which iPSC-derived hepatic stellate-like cells (iPS-HSCs) enveloped central hepatocyte-like cells[59]. The iHSOs revealed that quiescent iPS-HSCs sustain a cytokine-rich environment that promotes hepatocyte proliferation via the ICAM-1–IL-1β axis, while acetaminophen-induced hepatocyte injury activated stellate cells in a manner resembling human liver pathophysiology. This platform offers a valuable system for dissecting HSC–hepatocyte crosstalk and screening anti-fibrotic interventions[59]. Tadokoro et al. demonstrated that human iPSC-liver organoid transplantation reduces fibrosis through immunomodulation, providing evidence for the therapeutic application of organoid-derived cells in fibrotic liver disease[60]. Liu et al. reviewed the potential applications of organoid technology in liver regeneration after injury, highlighting the capacity of proliferating human hepatocyte organoids to restore liver function and promote regeneration in preclinical models[61].

7.4 Viral hepatitis models

HBV infection. Liver organoids provide a physiologically relevant platform for modeling hepatitis B virus (HBV) infection and studying virus–host interactions. Nie et al. generated multicellular liver organoids from human iPSCs by co-differentiating endodermal, mesenchymal, and endothelial lineages. These organoids expressed the HBV entry receptor NTCP at elevated levels and sustained HBV infection, as evidenced by the detection of covalently closed circular DNA (cccDNA), pregenomic RNA (pgRNA), viral proteins, and infectious progeny virus. HBV infection persisted for up to 20 days and was accompanied by dose-dependent alterations in hepatic function, demonstrating the utility of this model for investigating HBV–host interactions[62]. De Crignis et al. subsequently established a patient-derived liver organoid model using organoids from healthy donor liver tissue that could be infected with HBV derived from laboratory preparations or patient serum. Infected organoids supported key steps of viral replication, including cccDNA formation, HBV RNA and protein expression, HBeAg production, and release of infectious virus[63]. Moreover, organoids derived from non-tumorous cirrhotic liver tissue of HBV-infected patients exhibited an aberrant early cancer-associated transcriptional signature that clustered with hepatocellular carcinoma datasets, suggesting that patient-derived organoids may also provide a useful experimental system for investigating molecular events associated with HBV-related hepatocarcinogenesis[64].

HCV infection. Hepatitis C virus (HCV) infection can be successfully managed with antiviral therapies; however, steatotic liver injury and metabolic dysfunction may coexist in affected patients. Lee et al. developed a novel multicellular liver organoid model using a coculture system of macrophages and liver organoids differentiated from the same human pluripotent stem cell source[64]. The cocultured macrophages shifted toward a Kupffer-like phenotype, providing a suitable model for investigating steatotic liver injury in the context of HCV infection. HCV infection led to lipid accumulation in organoids by upregulating host lipogenesis, which was more marked with macrophage coculture. Reciprocally, long-term fatty acid treatment upregulated HCV amplification and promoted inflammation and fibrosis. Notably, the effects of three NASH drugs that have reached phase 3 clinical trials exhibited consistent results with clinical outcomes in this model, supporting its translational relevance[64].

HEV and other hepatotropic viruses. Liver organoids have also been applied to model hepatitis E virus (HEV) infection, enabling investigation of virus-host interactions and facilitating antiviral drug discovery in human liver-derived organoids[65].

7.5 Autoimmune liver disease models

Primary sclerosing cholangitis (PSC) is a heterogeneous and progressive fibroinflammatory cholangiopathy for which effective medical therapy remains elusive. Soroka et al. demonstrated that bile-derived organoids (BDOs) from patients with PSC recapitulate their inflammatory immune profile, expressing cholangiocyte markers and exhibiting distinct gene expression profiles compared with non-PSC controls, including enrichment of immune-related genes previously identified in genome-wide association studies of PSC[19]. Incubation of these organoids with IL-17A or TNF-α induced an immune-reactive phenotype with increased secretion of proinflammatory mediators, including CCL20, a T-cell chemoattractant. BDOs can be biobanked and sampled longitudinally over the disease course, providing a platform for mechanistic and therapeutic investigation[19]. Loarca et al. developed cholangioids from normal and diseased human cholangiocytes, demonstrating that PSC-derived cholangioids recapitulated cellular senescence, senescence-associated secretory phenotype, and macrophage recruitment[66]. Huang et al. contributed to the development of immune-competent organoid models for studying autoimmune hepatitis, enabling investigation of T cell-mediated hepatocyte injury and therapeutic intervention strategies.

7.6 Hereditary and metabolic liver disease models

Organoid technology has enabled disease modeling and therapeutic exploration across a range of hereditary and metabolic liver disorders. Patient-derived iPSC-hepatic organoids have been established for glycogen storage disease, citrullinemia type 1, and Wolman disease, recapitulating disease-specific metabolic phenotypes[25,27,67]. For Wilson disease, rescue of ATP7B function has been demonstrated in hepatocyte-like cells from patient iPSCs using gene therapy or chaperone drugs[68]. Nantasanti et al. established canine hepatic organoids with COMMD1 deficiency and demonstrated restoration of copper excretion upon lentiviral correction, providing proof-of-concept for autologous transplantation approaches[69].

In 2025, base editing technology was applied to correct a maple syrup urine disease (MSUD) mutation in patient-derived liver organoids. Zhang et al. generated hepatic organoids from iPSCs derived from an MSUD patient carrying a T322I mutation in the BCKDHB gene; the corrected organoids, achieved using the ABE8e adenine base editor with 100% editing efficiency at the mutation site and no detectable off-target edits, restored BCKDHA and BCKDHB expression and significantly reduced toxic branched-chain amino acid levels[70]. This study demonstrates the potential of combining base editing with liver organoid platforms for precision gene therapy of hereditary metabolic liver diseases.

7.7 Drug-induced liver injury models

Drug-induced liver injury (DILI) remains a leading cause of acute liver failure and drug withdrawal. Liver organoids provide a physiologically relevant platform for DILI prediction and mechanistic investigation[32]. Organoid-based DILI models benefit

from the expression of drug-metabolizing enzymes and transporters at levels closer to native liver than conventional two-dimensional (2D) hepatocyte cultures[71]. The incorporation of non-parenchymal cells, including immune and stromal components, may improve the modeling of complex DILI mechanisms that cannot be captured by hepatocyte-only systems. Igarashi et al. demonstrated that their expandable adult hepatocyte organoid system exhibited clinically coherent acetaminophen injury at relevant exposures, with damage rescued by N-acetylcysteine, mirroring the clinical antidote response[20].

7.8 Cholestatic disease models

Biliary organoids have been established from patients with biliary atresia, primary sclerosing cholangitis, and other cholestatic disorders. Amarachintha et al. demonstrated that biliary organoids from biliary atresia patients exhibited polarity changes, cilia misorientation, and reduced expression of developmental and functional markers; the phenotype was partially restored upon treatment with EGF and FGF2[72]. Shi et al. generated intrahepatic cholangiocyte organoids (ICOs) from PSC patients and demonstrated necroptosis induction, enabling screening for necroptosis inhibitors as a therapeutic strategy[73]. Reich et al. showed that bile-derived cholangioids from PSC patients exhibited decreased TGR5 expression, predisposing to more severe biliary injury; incubation with norUDCA restored TGR5 expression levels[74].

8 Translational applications and current evidence

8.1 Drug discovery, toxicology, and disease modeling

Much of the practical value of liver organoids still lies in research rather than routine clinical care. For drug discovery and toxicology, human organoid systems allow repeated perturbation, genetic manipulation, and medium-throughput testing while retaining more three-dimensional organization than conventional monolayer cultures[32,40,75]. PSC-derived and adult hepatocyte organoids have both been used in DILI assays, and multicellular or organoid-on-chip formats can add immune and perfusion-dependent mechanisms[20,32]. These advantages are useful, but they do not remove the need for benchmark compounds, assay-specific performance measures, and direct comparison with primary human hepatocytes.

The same principle applies to disease modeling: model composition should follow the biological question. Cancer organoids can retain clonal and regional heterogeneity; MASLD/MASH models can reproduce lipid accumulation and selected inflammatory or fibrotic responses; viral organoids can support defined host-pathogen interactions; and patient-derived models of hereditary disease retain causal genotypes[14,28,38,42,63,76]. Describing the specific phenotype reproduced by a model is more informative than treating any liver organoid as a miniature substitute for the whole organ.

8.2 Functional precision oncology

Patient-derived liver cancer organoids add a functional layer to genomic profiling because candidate therapies can be tested directly *ex vivo*. Liver-specific evidence now includes the LICOB pharmaco-proteogenomic resource and the large biobank reported by Yang et al.[41,42]. In the latter, organoid drug-response patterns corresponded with clinical responses in a small subset of relapsed patients. This is encouraging, but several obstacles remain: cultures can fail, sampling may miss intratumoral heterogeneity, turnaround time matters clinically, and assay methods are not yet standardized. Prospective liver-specific cohorts are still too limited for organoids to be considered routine decision tools.

8.3 Regenerative medicine and bioartificial liver systems

Expandable hepatocyte and progenitor organoids are also being investigated as sources for transplantation, tissue engineering, and extracorporeal liver support[45,60,77]. In animal studies, organoid-derived or iPSC-derived hepatic cells have shown regenerative or anti-fibrotic effects. Bioartificial liver systems take a different approach by combining viable hepatic tissue with an extracorporeal circuit. The UTOpiA system, which couples HLA-edited iPSC-derived hepatocyte-like organoids with granulocyte-monocyte apheresis, improved outcomes in rat models of acute and acute-on-chronic liver failure[78]. This is a notable preclinical result, but human studies are still required before organoid-based bioartificial liver support can be described as an established therapy[78,79].

8.4 Clinical readiness and evidence boundaries

The clinical maturity of liver organoid applications remains uneven[30]. Disease modeling and preclinical drug screening represent the most established applications, supported by extensive studies demonstrating that liver organoids can recapitulate disease-associated phenotypes and provide human-relevant platforms for pharmacological evaluation. In contrast, organoid-guided treatment selection, therapeutic transplantation, and bioartificial liver applications remain investigational and require further validation regarding reproducibility, scalability, safety, and long-term efficacy[80]. Therefore, the term "clinical practice" should be reserved for applications supported by prospective liver-specific evidence. Although clinical response-concordance studies from organoids of other tissues provide important proof-of-concept for the broader organoid field[81], they should not be interpreted as evidence that liver organoid platforms are ready for routine patient care.

9 Challenges, standardization, and ethical considerations

9.1 Biological and technical limitations

Current liver organoids reproduce only part of the architecture and cellular diversity of the native liver. Many lack a complete sinusoidal network, a functional biliary tree, zonated organization, or the full set of Kupffer, stellate, endothelial, and other immune or stromal cells[61]. Maturation is another persistent problem. PSC-derived hepatocyte-like cells often remain closer to fetal or intermediate states at the transcriptional and metabolic levels, which can limit studies of adult disease and xenobiotic metabolism[13,26]. Vascularized systems and newer adult hepatocyte organoids address some of these deficits, but no single model yet reproduces the structural and functional complexity of an adult human liver[20,21,25].

9.2 Reproducibility, scalability, and quality control

Reproducibility is shaped by many variables that are easy to overlook: donor background, extracellular matrix, growth-factor lots, passage number, differentiation efficiency, and operator technique all matter. Reports should therefore describe the source tissue, establishment rate, passage range, matrix and medium, cellular composition, genomic quality control, and relevant functional benchmarks, together with predefined assay acceptance criteria. Scale-up creates another set of problems. High-throughput or clinical-grade production requires automation, matrix replacement, closed-system manufacturing, cryopreservation, traceability, and cost control[45]. The resource estimates in Table 2 are meant as planning guidance, not as fixed prices.

9.3 Ethical and governance considerations

Ethical questions change with both the source of the organoid and its intended use. For human tissue-derived models, consent should address storage, future or secondary use, genomic analysis, data sharing, and, where relevant, commercial use and long-term biobanking. Patient-derived organoids can retain potentially identifiable genomic information, so privacy protection and controlled linkage to clinical records are important. ESC-derived systems raise additional issues related to embryo-derived cell sources; iPSC models avoid some of those concerns but still require appropriate consent and data governance. Genome-edited organoids add another layer, including off-target assessment, genomic stability, and a clear distinction between research use and therapeutic intent. If organoid-derived cells are considered for transplantation or bioartificial liver support, tumorigenicity, pathogen screening, manufacturing traceability, long-term safety, and equitable access become central regulatory and ethical questions. Animal tissues, xenografts, and transplantation studies should also follow the 3Rs (reduction, refinement, replacement) and relevant animal-welfare requirements[82].

Conflicts of interest deserve particular care in a narrative review because the authors determine which studies receive emphasis. Work developed by the authors or affiliated groups should be discussed in proportion to the wider literature, with limitations stated explicitly and without stronger clinical claims than the evidence supports. This is especially important when commercial affiliations or editorial roles are disclosed.

10 Comparative value of non-human liver organoids

10.1 Mouse and rat models

Mouse liver organoids are well suited to transgenic, gene-editing, and lineage-tracing experiments and can be established efficiently for mechanistic studies of development, regeneration, and tumor biology[3,83]. Rat organoids fit well with the large body of existing toxicology and pharmacology data[31]. Neither species, however, removes the translational gap: differences in metabolism, immunity, and disease biology mean that findings intended to inform human care should ultimately be tested in human-relevant systems.

10.2 Non-human primate models

Non-human primate liver organoids may provide an additional translational model for selected pharmacological and regenerative studies where species-specific physiology is particularly relevant. However, their application remains limited by restricted tissue availability, specialized infrastructure requirements, high costs, and ethical considerations[84]. Therefore, their use is most justified for focused questions that cannot be adequately addressed by human organoids, rodent models, or other alternative systems.

10.3 Cross-species comparison

Cross-species comparisons can be particularly informative when the aim is to separate conserved biology from species-specific responses[85]. They may also help explain why an effect seen in an animal model fails to reproduce in humans. Rather than ranking species along a single scale of "translational value", it is more useful to match each model to the question and use cross-species validation where it adds information.

11 Future directions

The liver organoid field continues to advance, with several directions demonstrating substantial promise (Fig. 4).

11.1 Vascularization, zonation, and organ complexity

One major technical goal is to reproduce the liver's spatial organization rather than only its cell types. Self-organizing sinusoidal vessel-like networks, multi-zonal organoids, and perfused microfluidic systems are beginning to capture nutrient gradients, shear stress, transport, and region-specific metabolism[21,25]. The next question is not simply whether such structures can be built, but whether they improve prediction of human disease or drug response enough to justify the additional complexity, cost, and variability.

11.2 Immune and stromal integration

Immune and stromal integration is equally important for questions involving inflammation, fibrosis, tumor immunity, or immune-mediated toxicity. Autologous macrophages, T cells, NK cells, stellate cells, and endothelial cells can add biological context that epithelial organoids lack[24,28,64]. Yet complexity has a price: more cell types introduce more sources of variability and can make it difficult to identify which population drives a phenotype. Cell-type-resolved readouts and defined co-culture composition will be essential if these models are to remain interpretable.

11.3 Gene editing and therapeutic modeling

CRISPR and base-editing approaches have made organoids useful both for testing gene function and for correcting inherited variants in patient-derived cells[38,86,87]. Their immediate strength lies in functional genomics and preclinical therapeutic modeling. Moving edited organoid-derived cells toward therapy will require a much higher bar, including rigorous genomic quality control, durable functional testing, reproducible manufacturing, and long-term safety data.

11.4 Automation, artificial intelligence, and organoid-on-chip platforms

Automation, advanced imaging, machine learning, and microfluidic technologies may help overcome several practical barriers that currently limit organoid scalability and reproducibility[88]. Automated culture systems can reduce operator-

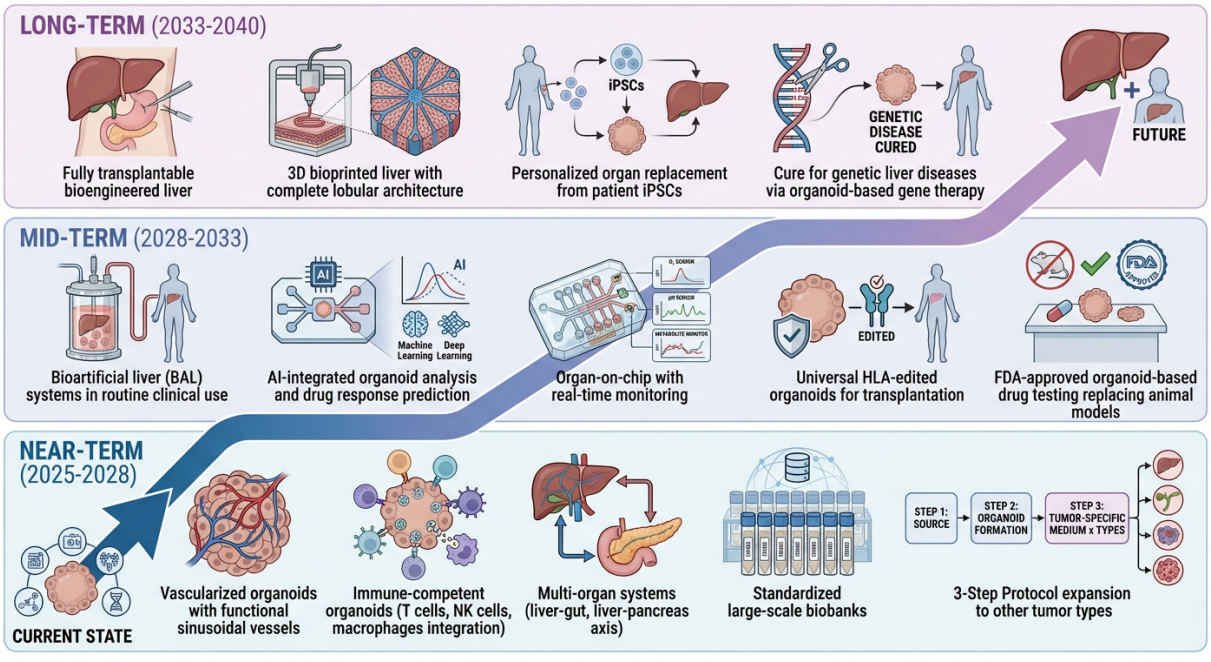


Figure 4. Future perspectives for liver organoid development from 2026 to 2040. From the current state (basic organoids) progressing through near-term goals (vascularized organoids, immune-competent models) to the long-term vision (bioartificial liver devices, transplantable artificial organs). The timeline illustrates anticipated advances from 2026 to 2040.

dependent variation and enable higher-throughput workflows, whereas computational imaging approaches facilitate longitudinal phenotyping and standardized morphological assessment[89]. Microfluidic platforms further allow controlled environmental regulation and dynamic drug exposure[90]. However, the value of these approaches will depend on transparent model development, independent validation, and biologically interpretable readouts[91]. In large-scale organoid biobanks, computational tools may become increasingly important for data integration and quality assessment, but they should complement rather than replace experimental validation[88].

11.5 Outstanding questions

Several unresolved problems will determine how far the field can move (Fig. 4). Adult-like hepatocyte function must become more reproducible without sacrificing expandability. It is still unclear how much vascular, biliary, immune, and stromal complexity is necessary for a given biological or pharmacological question. Quality-control measures also need to predict performance across laboratories rather than only within a single protocol. In cancer, the key test will be whether organoid pharmacotyping improves patient outcomes prospectively beyond existing clinical and molecular tools. Regenerative and bioartificial liver systems face an even higher threshold: durable safety, efficacy, scale-up, and manufacturability will all have to be demonstrated in humans. Progress on these questions will depend on multicenter benchmarking and prospective validation, not on technical complexity alone.

12 Conclusions

Liver organoids now fill an important space between conventional cell culture, animal models, and access to human liver tissue. Their strongest evidence base remains in mechanistic research, disease modeling, and preclinical drug or toxicity studies. Patient-derived cancer organoids, multicellular disease models, adult hepatocyte organoids, vascularized cultures, and organoid-on-chip systems broaden what can be studied, but each captures only part of liver biology. None should be treated as a complete *in vitro* liver.

The next phase of the field will be judged less by how complex an organoid looks and more by whether the model is reproducible, fit for the question, and validated against relevant human data. Standardized quality control, realistic attention to cost, and appropriate ethical governance will be as important as further gains in maturation or vascularization. Classifying liver organoids by cell source, complexity, microenvironment, maturation, and intended use offers a practical way to compare systems without assuming that one format is universally superior. With liver-specific prospective validation, some of these models may eventually support routine clinical decisions; for now, their clearest role is as powerful research and translational tools.

Research ethics and patient consent

Not applicable. This review did not involve new experiments with human participants or animals. Ethical and governance issues relevant to human tissue, stem cells, genome editing, biobanking, transplantation, and animal models are discussed in Section 9.3.

Availability of data and materials

No new datasets were generated or analyzed in this narrative review. The information discussed is drawn from the cited literature.

Declaration of conflicting interests

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Authors' contributions

Y.T.F. and X.Z. conducted a literature review on liver biology and drafted hepatic-related sections. J.W. Performed organoid technology research and wrote methodology content. X.X.H. designed the review framework and supervised the project. All authors participated in writing, reviewing, and approving the final manuscript.

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References

[1] Asrani, S. K., Devarbhavi, H., Eaton, J., Kamath, P. S. Burden of liver diseases in the world. *Journal of Hepatology*, **2019**, 70(1): 151–171. https://doi.org/10.1016/j.jhep.2018.09.014

[2] Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., Bray, F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*, **2021**, 71(3): 209–249. https://doi.org/10.3322/caac.21660

[3] Huch, M., Dorrell, C., Boj, S. F., van Es, J. H., Li, V. S. W., van de Wetering, M., Sato, T., Hamer, K., Sasaki, N., Finegold, M. J. et al. *In vitro* expansion of single Lgr5+ liver stem cells induced by Wnt-driven regeneration. *Nature*, **2013**, 494(7436): 247−250. https://doi.org/10.1038/nature11826

[4] Sun, X. C., Kong, D. F., Zhao, J., Faber, K. N., Xia, Q., He, K. Liver organoids: Established tools for disease modeling and drug development. *Hepatology Communications*, **2023**, 7(4): e0105. https://doi.org/10.1097/hc9.0000000000000105

[5] Sato, T., Vries, R. G., Snippert, H. J., van de Wetering, M., Barker, N., Stange, D. E., van Es, J. H., Abo, A., Kujala, P., Peters, P. J. et al. Single Lgr5 stem cells build crypt-villus structures *in vitro* withoutamesenchymalniche.*Nature*,**2009**,459(7244):262–265.https://doi.org/10.1038/nature07935

[6] Takebe, T., Sekine, K., Enomura, M., Koike, H., Kimura, M., Ogaeri, T., Zhang, R. R., Ueno, Y., Zheng, Y. W., Koike, N. et al. Vascularized and functional human liver from an iPSC-derived organ bud transplant. *Nature*, **2013**, 499(7459): 481–484. https://doi.org/10.1038/nature12271

[7] Koike, H., Iwasawa, K., Ouchi, R. E., Maezawa, M., Giesbrecht, K., Saiki, N., Ferguson, A., Kimura, M., Thompson, W. L., Wells, J. M. et al. Modelling human hepato-biliary-pancreatic organogenesis from the foregut–midgut boundary. *Nature*, **2019**, 574(7776): 112–116. https://doi.org/10.1038/s41586-019-1598-0

[8] Sljukic, A., Green Jenkinson, J., Niksic, A., Prior, N., Huch, M. Advances in liver and pancreas organoids: How far we have come and where we go next. *Nature Reviews Gastroenterology & Hepatology*, **2026**, 23(1): 44–64. https://doi.org/10.1038/s41575-025-01116-1

[9] Prior, N., Hindley, C. J., Rost, F., Meléndez, E., Lau, W. W. Y., Göttgens, B., Rulands, S., Simons, B. D., Huch, M. Lgr5+ stem and progenitor cells reside at the apex of a heterogeneous embryonic hepatoblast pool. *Development*, **2019**, 146(12): dev174557. https://doi.org/10.1242/dev.174557

[10] Huch, M., Gehart, H., van Boxtel, R., Hamer, K., Blokzijl, F., Verstegen, M. M. A., Ellis, E., van Wenum, M., Fuchs, S. A., de Ligt, J. et al. Long-term culture of genome-stable bipotent stem cells from adult human liver. *Cell*, **2015**, 160(1–2): 299–312. https://doi.org/10.1016/j.cell.2014.11.050

[11] Takebe, T., Sekine, K., Kimura, M., Yoshizawa, E., Ayano, S., Koido, M., Funayama, S., Nakanishi, N., Hisai, T., Kobayashi, T. et al. Massive and reproducible production of liver buds entirely from human pluripotent stem cells. *Cell Reports*, **2017**, 21(10): 2661–2670. https://doi.org/10.1016/j.celrep.2017.11.005

[12] Nuciforo, S., Fofana, I., Matter, M. S., Blumer, T., Calabrese, D., Boldanova, T., Piscuoglio, S., Wieland, S., Ringnalda, F., Schwank, G. et al. Organoid models of human liver cancers derived from tumor needle biopsies. *Cell Reports*, **2018**, 24(5): 1363–1376. https://doi.org/10.1016/j.celrep.2018.07.001

[13] Hu, H. L., Gehart, H., Artegiani, B., LÖpez-Iglesias, C., Dekkers, F., Basak, O., van Es, J., Chuva de Sousa Lopes, S. M., Begthel, H., Korving, J. et al. Long-term expansion of functional mouse and human hepatocytes as 3D organoids. *Cell*, **2018**, 175(6): 1591–1606.e19. https://doi.org/10.1016/j.cell.2018.11.013

[14] Broutier, L., Mastrogiovanni, G., Verstegen, M. M., Francies, H. E., Gavarró, L. M., Bradshaw, C. R., Allen, G. E., Arnes-Benito, R., Sidorova, O., Gaspersz, M. P. et al. Human primary liver cancer–derived organoid cultures for disease modeling and drug screening. *Nature Medicine*, **2017**, 23(12): 1424–1435. https://doi.org/10.1038/nm.4438

[15] Saltsman, J. A., Hammond, W. J., Narayan, N. J. C., Requena, D., Gehart, H., Lalazar, G., LaQuaglia, M. P., Clevers, H., Simon, S. A human organoid model of aggressive hepatoblastoma for disease modeling and drug testing. *Cancers*, **2020**, 12(9): 2668. https://doi.org/10.3390/cancers12092668

[16] Wang, T. P., Qu, X. T., Si, J. H., Meng, J. K., Zhang, T., Niu, S. L. Liver organoids: From disease modelling to regenerative medicine. *Cell Proliferation*, **2026**: e70268. https://doi.org/10.1111/cpr.70268

[17] Wang, S. Y., Wang, X., Tan, Z. L., Su, Y. X., Liu, J., Chang, M. Y., Yan, F., Chen, J., Chen, T., Li, C. J. et al. Human ESC-derived expandable hepatic organoids enable therapeutic liver repopulation and pathophysiological modeling of alcoholic liver injury. *Cell Research*, **2019**, 29(12): 1009–1026. https://doi.org/10.1038/s41422-019-0242-8

[18] Shao, W. D., Xu, H., Zeng, K. H., Ye, M. Z., Pei, R. J., Wang, K. Advances in liver organoids: Replicating hepatic complexity for toxicity assessment and disease modeling. *Stem Cell Research & Therapy*, **2025**, 16: 27. https://doi.org/10.1186/s13287-025-04139-2

[19] Soroka, C. J., Assis, D. N., Alrabadi, L. S., Roberts, S., Cusack, L., Jaffe, A. B., Boyer, J. L. Bile-derived organoids from patients with primary sclerosing cholangitis recapitulate their inflammatory immune profile. *Hepatology*, **2019**, 70(3): 871–882. https://doi.org/10.1002/hep.30470

[20] Igarashi, R., Oda, M., Okada, R., Yano, T., Takahashi, S., Pastuhov, S., Matano, M., Masuda, N., Togasaki, K., Ohta, Y. et al. Generation of human adult hepatocyte organoids with metabolic functions. *Nature*, **2025**, 641(8065): 1248–1257. https://doi.org/10.1038/s41586-025-08861-y

[21] Al Reza, H., Santangelo, C., Iwasawa, K., Al Reza, A., Sekiya, S., Glaser, K., Bondoc, A., Merola, J., Takebe, T. Multi-zonal liver organoids from human pluripotent stem cells. *Nature*, **2025**, 641(8065): 1258–1267. https://doi.org/10.1038/s41586-025-08850-1

[22] Rezvani, M., Quach, S., Lewis, K., Saiki, N., Xue, C. Q., Kimura, M., Iwasawa, K., Weihs, J., Elzobair, T., Al Reza, H. et al. Modeling immune lineage co-development in human pluripotent stem cell-derived liver organoids. *Journal of Hepatology*, **2026**, 84(5): 946–961. https://doi.org/10.1016/j.jhep.2025.11.018

[23] Kim, Y., Kang, M., Mamo, M. G., Adisasmita, M., Huch, M., Choi,

D. Liver organoids: Current advances and future applications for hepatology. *Clinical and Molecular Hepatology*, **2025**, 31: S327–S348. https://doi.org/10.3350/cmh.2024.1040

[24] Guan, Y., Enejder, A., Wang, M. Y., Fang, Z. Q., Cui, L., Chen, S. Y., Wang, J. X., Tan, Y. L., Wu, M. H., Chen, X. Y. et al. A human multi-lineage hepatic organoid model for liver fibrosis. *Nature Communications*, **2021**, 12: 6138. https://doi.org/10.1038/s41467-021-26410-9

[25] Saiki, N., Nio, Y., Yoneyama, Y., Kawamura, S., Iwasawa, K., Kawakami, E., Araki, K., Fukumura, J., Sakairi, T., Kono, T. et al. Self-organization of sinusoidal vessels in pluripotent stem cell-derived human liver bud organoids. *Nature Biomedical Engineering*, **2025**, 9(11): 1869–1885. https://doi.org/10.1038/s41551-025-01416-6

[26] Mun, S. J., Ryu, J. S., Lee, M. O., Son, Y. S., Oh, S. J., Cho, H. S., Son, M. Y., Kim, D. S., Kim, S. J., Yoo, H. J. et al. Generation of expandable human pluripotent stem cell-derived hepatocyte-like liver organoids. *Journal of Hepatology*, **2019**, 71(5): 970–985. https://doi.org/10.1016/j.jhep.2019.06.030

[27] Liu, S., Wang, Z., Zhu, L. Y., Wang, L. B., Zhao, T. Y., Han, P. S., Xu, Y. D., Yang, L., Hu, L., Yan, F. Y. et al. Generation and applications of an expandable and mature hiPSC-derived liver organoid.*ActaPharmaceuticaSinicaB*,**2025**,15(12):6382–6398.https://doi.org/10.1016/j.apsb.2025.09.029

[28] Ouchi, R., Togo, S., Kimura, M., Shinozawa, T., Koido, M., Koike, H., Thompson, W., Karns, R. A., Mayhew, C. N., McGrath, P. S. et al. Modeling steatohepatitis in humans with pluripotent stem cell-derived organoids. *Cell Metabolism*, **2019**, 30(2): 374–384.e6. https://doi.org/10.1016/j.cmet.2019.05.007

[29] Sun, L., Zhang, Y. Y., Niu, Y. D., Yang, H., Zhou, L., Jia, X. D., Chen, Y. H., Liu, Z. Q., Wang, T. T., Liang, K. N. et al. Multi-lineage hepatic organoids reveal toxic exosome mediated indirect hepatotoxicity. *Nature Communications*, **2026**, 17: 2926. https://doi.org/10.1038/s41467-026-69548-0

[30] Wang, Y. H., Ye, Z. C., Lin, Y. H., Zhao, Y. J., Zhong, D. Y., Chen, J., Yin, J., Yan, J. N., Wang, Y. F. The promise and potential of liver organoids: Development, classification and application. *TransMed*, **2026**, 1(1): 100003. https://doi.org/10.1016/j.tmed.2026.100003

[31] Kuijk, E. W., Rasmussen, S., Blokzijl, F., Huch, M., Gehart, H., Toonen, P., Begthel, H., Clevers, H., Geurts, A. M., Cuppen, E. Generation and characterization of rat liver stem cell lines and their engraftment in a rat model of liver failure. *Scientific Reports*, **2016**, 6: 22154. https://doi.org/10.1038/srep22154

[32] Shinozawa, T., Kimura, M., Cai, Y. Q., Saiki, N., Yoneyama, Y., Ouchi, R., Koike, H., Maezawa, M., Zhang, R. R., Dunn, A. et al. High-fidelity drug-induced liver injury screen using human pluripotent stem cell–derived organoids. *Gastroenterology*, **2021**, 160(3): 831–846.e10. https://doi.org/10.1053/j.gastro.2020.10.002

[33] Broutier, L., Andersson-Rolf, A., Hindley, C. J., Boj, S. F., Clevers, H., Koo, B. K., Huch, M. Culture and establishment of self-renewing human and mouse adult liver and pancreas 3D organoids and their geneticmanipulation.*NatureProtocols*,**2016**,11(9):1724–1743.https://doi.org/10.1038/nprot.2016.097

[34] Nelson, D. R., Zeldin, D. C., Hoffman, S. M., Maltais, L. J., Wain, H. M., Nebert, D. W. Comparison of cytochrome P450 (CYP) genes from the mouse and human genomes, including nomenclature recommendations for genes, pseudogenes and alternative-splice variants. *Pharmacogenetics*, **2004**, 14(1): 1–18. https://doi.org/10.1097/00008571-200401000-00001

[35] Xu, D., Nishimura, T., Nishimura, S., Zhang, H. L., Zheng, M., Guo, Y. Y., Masek, M., Michie, S. A., Glenn, J., Peltz, G. Fialuridine induces acute liver failure in chimeric TK-NOG mice: A model for detecting hepatic drug toxicity prior to human testing. *PLoS Medicine*, **2014**, 11(4): e1001628. https://doi.org/10.1371/journal.pmed.1001628

[36] Jiang, C. F., Wang, D., Ni, C., Li, X., Liu, X. Y., Ge, X. M., Chen, D. M., Dzakah, E. E., Zhao, B. Generation of cynomolgus monkey airway, liver ductal, and kidney organoids with pharmacokinetic functions. *Organs-on-a-Chip*, **2023**, 5: 100031. https://doi.org/10.1016/j.ooc.2023.100031

[37] Shimizu, N., Shiraishi, H., Hanada, T. Zebrafish as a useful model system for human liver disease. *Cells*, **2023**, 12(18): 2246. https://doi.org/10.3390/cells12182246

[38] Guan, Y., Xu, D., Garfin, P. M., Ehmer, U., Hurwitz, M., Enns, G., Michie, S., Wu, M. H., Zheng, M., Nishimura, T. et al. Human hepatic organoids for the analysis of human genetic diseases. *JCI Insight*, **2017**, 2(17): e94954. https://doi.org/10.1172/jci.insight.94954

[39] Leite, S. B., Roosens, T., El Taghdouini, A., Mannaerts, I., Smout, A. J., Najimi, M., Sokal, E., Noor, F., Chesne, C., van Grunsven, L. A. Novel human hepatic organoid model enables testing of drug-induced liver fibrosis *in vitro*. *Biomaterials*, **2016**, 78: 1–10. https://doi.org/10.1016/j.biomaterials.2015.11.026

[40] Bin Ramli, M. N., Lim, Y. S., Koe, C. T., Demircioglu, D., Tng, W., Gonzales, K. A. U., Tan, C. P., Szczerbinska, I., Liang, H. Q., Soe, E. L. et al. Human pluripotent stem cell-derived organoids as models ofliverdisease.*Gastroenterology*,**2020**,159(4):1471–1486.e12.https://doi.org/10.1053/j.gastro.2020.06.010

[41] Ji, S. Y., Feng, L., Fu, Z. L., Wu, G. H., Wu, Y. C., Lin, Y. P., Lu, D. Y., Song, Y. L., Cui, P., Yang, Z. J. et al. Pharmaco-proteogenomic characterization of liver cancer organoids for precision oncology. *Science Translational Medicine*, **2023**, 15(706): eadg3358. https://doi.org/10.1126/scitranslmed.adg3358

[42] Yang, H., Cheng, J. H., Zhuang, H., Xu, H. C., Wang, Y. N., Zhang, T. T., Yang, Y. M., Qian, H. G., Lu, Y. Y., Han, F. et al. Pharmacogenomic profiling of intra-tumor heterogeneity using a large organoid biobank of liver cancer. *Cancer Cell*, **2024**, 42(4): 535–551.e8. https://doi.org/10.1016/j.ccell.2024.03.004

[43] Dowbaj, A. M., Sljukic, A., Niksic, A., Landerer, C., Delpierre, J., Yang, H. C., Lahree, A., Kühn, A. C., Beers, D., Byrne, H. M. et al. Mouse liver assembloids model periportal architecture and biliary fibrosis. *Nature*, **2025**, 644(8076): 473–482. https://doi.org/10.1038/s41586-025-09183-9

[44] Pohlberger, R. F., Hardt, K. S., Kühnel, M. P., Palzer, J., Reinhardt, J. L., Beetz, O., Oldhafer, F., Meister, F. A., Just, K. S., Schröder-Lange, S. K. et al. From patient liver tissue to organoids: Establishment of a translational platform using healthy, steatotic, and cirrhotic tissue sources. *Cells*, **2026**, 15(5): 432. https://doi.org/10.3390/cells15050432

[45] Schneeberger, K., Sánchez-Romero, N., Ye, S. C., van Steenbeek, F. G., Oosterhoff, L. A., Pla Palacin, I., Chen, C., van Wolferen, M. E., van Tienderen, G., Lieshout, R. et al. Large-scale production of LGR5-positive bipotential human liver stem cells. *Hepatology*, **2020**, 72(1): 257–270. https://doi.org/10.1002/hep.31037

[46] Li, X. D., Francies, H. E., Secrier, M., Perner, J., Miremadi, A., Galeano-Dalmau, N., Barendt, W. J., Letchford, L., Leyden, G. M., Goffin, E. K. et al. Organoid cultures recapitulate esophageal adenocarcinoma heterogeneity providing a model for clonality studies and precision therapeutics. *Nature Communications*, **2018**, 9: 2983. https://doi.org/10.1038/s41467-018-05190-9

[47] Rumgay, H., Ferlay, J., de Martel, C., Georges, D., Ibrahim, A. S., Zheng, R. S., Wei, W. Q., Lemmens, V. E. P. P., Soerjomataram, I. Global, regional and national burden of primary liver cancer by subtype. *European Journal of Cancer*, **2022**, 161: 108–118. https://doi.org/10.1016/j.ejca.2021.11.023

[48] Kim, C. Y., Kim, S. C., Shin, R., Kim, M. J., Jeong, S. Y., Park, J. W., Ku, J. L. Integrative multi-omics of matched primary and liver metastatic colorectal cancer organoids identifies putative molecular targets. *Translational Oncology*, **2026**, 63: 102592. https://doi.org/10.1016/j.tranon.2025.102592

[49] Zhou, J. M., Dai, W. X., Wang, R. J., Xu, W. Q., Xiang, Z., Wang, Y. X., Zhang, T., Zhao, Y. M., Wang, L., Mao, A. R. Organoid modeling identifies USP3-AS1 as a novel promoter in colorectal cancer liver metastasis through increasing glucose-driven histone

lactylation.*ActaPharmacologicaSinica*,**2025**,46(5):1404–1418.https://doi.org/10.1038/s41401-024-01465-8

[50] van Son, G. J. F., Ringnalda, F. C. A. S., van Roosmalen, M. J., Kluiver, T. A., Hansen, Q., Duiker, E., van den Heuvel, M. C., de Meijer, V. E., de Kleine, R. H., de Krijger, R. R. et al. A fully annotated hepatoblastoma tumoroid biobank details treatment-induced evolution and clonal dynamics in paediatric cancer patients. *Organoids*, **2026**, 5(1): 4. https://doi.org/10.3390/organoids5010004

[51] Ooft, S. N., Weeber, F., Dijkstra, K. K., McLean, C. M., Kaing, S., van Werkhoven, E., Schipper, L., Hoes, L., Vis, D. J., van de Haar, J. et al. Patient-derived organoids can predict response to chemotherapy in metastatic colorectal cancer patients. *Science Translational Medicine*, **2019**, 11(513): eaay2574. https://doi.org/10.1126/scitranslmed.aay2574

[52] Du, L. W., Dong, J. X., Du, S. D. Organoid models for T cell-based immunotherapy in hepatobiliary cancers. *Hepatobiliary Surgery and Nutrition*, **2025**, 14(6): 1042–1044. https://doi.org/10.21037/hbsn-2025-aw-863

[53] Tilg, H., Petta, S., Stefan, N., Targher, G. Metabolic dysfunction–associated steatotic liver disease in adults: A review. *JAMA*, **2026**, 335(2): 163. https://doi.org/10.1001/jama.2025.19615

[54] Gurevich, I., Burton, S. A., Munn, C., Ohshima, M., Goedland, M. E., Czysz, K., Rajesh, D. iPSC-derived hepatocytes generated from NASH donors provide a valuable platform for disease modeling and drug discovery. *Biology Open*, **2020**: bio.055087. https://doi.org/10.1242/bio.055087

[55] McCarron, S., Bathon, B., Conlon, D. M., Abbey, D., Rader, D. J., Gawronski, K., Brown, C. D., Olthoff, K. M., Shaked, A., Raabe, T. D. Functional characterization of organoids derived from irreversibly damaged liver of patients with NASH. *Hepatology*, **2021**, 74(4): 1825–1844. https://doi.org/10.1002/hep.31857

[56] Rezvani, M., Vallier, L., Guillot, A. Modeling nonalcoholic fatty liver disease in the dish using human-specific platforms: Strategies and limitations. *Cellular and Molecular Gastroenterology and Hepatology*, **2023**, 15(5): 1135–1145. https://doi.org/10.1016/j.jcmgh.2023.01.014

[57] Goswami, Y., Baghel, A., Sharma, G., Sharma, P. K., Biswas, S., Yadav, R., Garg, P. K., Shalimar, Tandon, R. Liver organoids from hepatocytes of healthy humans and non-alcoholic fatty liver disease (NAFLD) patients display multilineage architecture and can be used to develop an *in vitro* model of steatohepatitis. *Journal of Clinical and Experimental Hepatology*, **2025**, 15(3): 102463. https://doi.org/10.1016/j.jceh.2024.102463

[58] Hendriks, D., Brouwers, J. F., Hamer, K., Geurts, M. H., Luciana, L., Massalini, S., López-Iglesias, C., Peters, P. J., Rodríguez-Colman, M. J., Chuva de Sousa Lopes, S. et al. Engineered human hepatocyte organoids enable CRISPR-based target discovery and drug screening for steatosis. *Nature Biotechnology*, **2023**, 41(11): 1567–1581. https://doi.org/10.1038/s41587-023-01680-4

[59] Mochida, T., Miyoshi, M., Kakinuma, S., Shimizu, T., Tsuchiya, J., Watakabe, K., Inada, K., Kaneko, S., Kawai-Kitahata, F., Murakawa, M. et al. Crosstalk *via* ICAM-1 enhances supportive phenotype of stellate cells and drives hepatocyte proliferation in iPSC-derived hepatic organoids. *Stem Cell Reports*, **2025**, 20(10): 102642. https://doi.org/10.1016/j.stemcr.2025.102642

[60] Tadokoro, T., Murata, S., Kato, M., Ueno, Y., Tsuchida, T., Okumura, A., Kuse, Y., Konno, T., Uchida, Y., Yamakawa, Y. et al. Human iPSC–liver organoid transplantation reduces fibrosis through immunomodulation. *Science Translational Medicine*, **2024**, 16(757): eadg0338. https://doi.org/10.1126/scitranslmed.adg0338

[61] Liu, Q., Wang, S. Y., Fu, J., Chen, Y., Xu, J., Wei, W. J., Song, H., Zhao, X. F., Wang, H. Y. Liver regeneration after injury: Mechanisms, cellular interactions and therapeutic innovations. *Clinical and Translational Medicine*, **2024**, 14(8): e1812. https://doi.org/10.1002/ctm2.1812

[62] Nie, Y. Z., Zheng, Y. W., Miyakawa, K., Murata, S., Zhang, R. R., Sekine, K., Ueno, Y., Takebe, T., Wakita, T., Ryo, A. et al. Recapitulation of hepatitis B virus–host interactions in liver organoids from human induced pluripotent stem cells. *EBioMedicine*, **2018**, 35: 114–123. https://doi.org/10.1016/j.ebiom.2018.08.014

[63] De Crignis, E., Hossain, T., Romal, S., Carofiglio, F., Moulos, P., Khalid, M. M., Rao, S., Bazrafshan, A., Verstegen, M. M., Pourfarzad, F. et al. Application of human liver organoids as a patient-derived primary model for HBV infection and related hepatocellular carcinoma. *eLife*, **2021**, 10: e60747. https://doi.org/10.7554/elife.60747

[64] Lee, J., Gil, D., Park, H., Lee, Y., Mun, S. J., Shin, Y., Jo, E., Windisch, M. P., Kim, J. H., Son, M. J. A multicellular liver organoid model for investigating hepatitis C virus infection and nonalcoholic fatty liver disease progression. *Hepatology*, **2024**, 80(1): 186–201. https://doi.org/10.1097/hep.0000000000000683

[65] Li, P. F., Li, Y. L., Wang, Y. J., Liu, J. Y., Lavrijsen, M., Li, Y., Zhang, R. Y., Verstegen, M. M. A., Wang, Y. N., Li, T. C. et al. Recapitulating hepatitis E virus–host interactions and facilitating antiviral drug discovery in human liver–derived organoids. *Science Advances*, **2022**, 8(3): eabj5908. https://doi.org/10.1126/sciadv.abj5908

[66] Loarca, L., De Assuncao, T. M., Jalan-Sakrikar, N., Bronk, S., Krishnan, A., Huang, B., Morton, L., Trussoni, C., Bonilla, L. M., Krueger, E. et al. Development and characterization of cholangioids from normal and diseased human cholangiocytes as an *in vitro* model to study primary sclerosing cholangitis. *Laboratory Investigation*, **2017**, 97(11): 1385–1396. https://doi.org/10.1038/labinvest.2017.63

[67] Yan, H. H. N., Siu, H. C., Law, S., Ho, S. L., Yue, S. S. K., Tsui, W. Y., Chan, D., Chan, A. S., Ma, S., Lam, K. O. et al. A comprehensive human gastric cancer organoid biobank captures tumor subtype heterogeneity and enables therapeutic screening. *Cell Stem Cell*, **2018**, 23(6): 882–897.e11. https://doi.org/10.1016/j.stem.2018.09.016

[68] Zhang, S. Q., Chen, S., Li, W., Guo, X. P., Zhao, P., Xu, J. Y., Chen, Y., Pan, Q., Liu, X. R., Zychlinski, D. et al. Rescue of ATP7B function in hepatocyte-like cells from Wilson's disease induced pluripotent stem cells using gene therapy or the chaperone drug curcumin.*HumanMolecularGenetics*,**2011**,20(16):3176–3187.https://doi.org/10.1093/hmg/ddr223

[69] Nantasanti, S., Spee, B., Kruitwagen, H. S., Chen, C., Geijsen, N., Oosterhoff, L. A., van Wolferen, M. E., Pelaez, N., Fieten, H., Wubbolts, R. W. et al. Disease modeling and gene therapy of copper storage disease in canine hepatic organoids. *Stem Cell Reports*, **2015**, 5(5): 895–907. https://doi.org/10.1016/j.stemcr.2015.09.002

[70] Zhang, H. Y., Wan, Z. R., Li, X. M., Wang, B., Guan, J. Y., Li, Y., Jin, X. H., Ma, X., Liu, G. H. Adenine base editing rescues disrupted BCKDH function and reduces BCAAs toxic accumulation in maple syrup urine disease patient iPSC-hepatic organoids. *Stem Cell Research & Therapy*, **2025**, 16: 512. https://doi.org/10.1186/s13287-025-04630-w

[71] Liu, Y. C., Zhou, Y. X., Ahodantin, J., Jin, Y., Zhu, J. J., Sun, Z. H., Wu, X. L., Su, L. S., Yang, Y. Z. Generation and characterization of mature hepatocyte organoids for liver metabolic studies. *Journal of Cell Science*, **2024**, 137(10): jcs261961. https://doi.org/10.1242/jcs.261961

[72] Amarachintha, S. P., Mourya, R., Ayabe, H., Yang, L., Luo, Z. H., Li, X. F., Thanekar, U., Shivakumar, P., Bezerra, J. A. Biliary organoids uncover delayed epithelial development and barrier function in biliary atresia. *Hepatology*, **2022**, 75(1): 89–103. https://doi.org/10.1002/hep.32107

[73] Shi, S. J., Verstegen, M. M. A., Roest, H. P., Ardisasmita, A. I., Cao, W. L., Roos, F. J. M., de Ruiter, P. E., Niemeijer, M., Pan, Q. W., IJzermans, J. N. M. et al. Recapitulating cholangiopathy-associated necroptotic cell death *in vitro* using human cholangiocyte organoids. *Cellular and Molecular Gastroenterology and Hepatology*, **2022**, 13(2): 541–564. https://doi.org/10.1016/j.jcmgh.2021.10.009

[74] Reding, B., Carter, P., Qi, Y. J., Li, Z., Wu, Y., Wannemuehler, M., Bratlie, K. M., Wang, Q. Manipulate intestinal organoids with niobium carbide nanosheets. *Journal of Biomedical Materials Research Part A*, **2021**, 109(4): 479–487. https://doi.org/10.1002/jbm.a.37032

[75] Prior, N., Inacio, P., Huch, M. Liver organoids: From basic research to therapeutic applications. *Gut*, **2019**, 68(12): 2228–2237. https://doi.org/10.1136/gutjnl-2019-319256

[76] Hindson, J. Human hepatocyte organoids model early NAFLD. *NatureReviewsGastroenterology&Hepatology*,**2023**,20(5):269.https://doi.org/10.1038/s41575-023-00776-1

[77] Verstegen, M. M. A., Willemse, J., van den Hoek, S., Kremers, G. J., Luider, T. M., van Huizen, N. A., Willemssen, F. E. J. A., Metselaar, H. J., IJzermans, J. N. M., van der Laan, L. J. W. et al. Decellularization of whole human liver grafts using controlled perfusion for transplantable organ bioscaffolds. *Stem Cells and Development*, **2017**, 26(18): 1304–1315. https://doi.org/10.1089/scd.2017.0095

[78] Yamaguchi, H., Yoneyama, Y., Ichimura, K., Ohtsu, K., Soen, M., Moriya, C., Kumagai, M., Myers, R. P., Subramanian, G. M., Takebe, T. Reversal of ACLF and ALF using whole blood extracorporeal system combining HLA-depleted liver organoids with granulocyte-monocyte apheresis. *Journal of Hepatology*, **2026**, 84(2): 293–307. https://doi.org/10.1016/j.jhep.2025.08.038

[79] Wu, J. Q., Hui, L. J. Bioartificial liver system for liver failure: A therapeutic UTOpiA on the horizon. *Journal of Hepatology*, **2026**, 84(2): 248–250. https://doi.org/10.1016/j.jhep.2025.10.002

[80] Luce, E., Messina, A., Duclos-Vallée, J. C. Hepatic organoids as a platform for liver disease modeling and the development of novel therapies. *Clinics and Research in Hepatology and Gastroenterology*, **2025**, 49(7): 102647. https://doi.org/10.1016/j.clinre.2025.102647

[81] Vlachogiannis, G., Hedayat, S., Vatsiou, A., Jamin, Y., Fernández-Mateos, J., Khan, K., Lampis, A., Eason, K., Huntingford, I., Burke, R. et al. Patient-derived organoids model treatment response of metastatic gastrointestinal cancers. *Science*, **2018**, 359(6378): 920–926. https://doi.org/10.1126/science.aao2774

[82] Lovell-Badge, R., Anthony, E., Barker, R. A., Bubela, T., Brivanlou, A. H., Carpenter, M., Charo, R. A., Clark, A., Clayton, E., Cong, Y. L. et al. ISSCR guidelines for stem cell research and clinical translation: The 2021 update. *Stem Cell Reports*, **2021**, 16(6): 1398–1408. https://doi.org/10.1016/j.stemcr.2021.05.012

[83] Cao, W. L., Liu, J. Y., Wang, L., Li, M., Verstegen, M. M. A., Yin, Y. B., Ma, B. Y., Chen, K., Bolkestein, M., Sprengers, D. et al. Modeling liver cancer and therapy responsiveness using organoids derived from primary mouse liver tumors. *Carcinogenesis*, **2019**, 40(1): 145–154. https://doi.org/10.1093/carcin/bgy129

[84] ten Dam, M. J. M., Frederix, G. W. J., ten Ham, R. M. T., van der Laan, L. J. W., Schneeberger, K. Toward transplantation of liver organoids: From biology and ethics to cost-effective therapy. *Transplantation*, **2023**, 107(8): 1706–1717. https://doi.org/10.1097/tp.0000000000004520

[85] Kruitwagen, H. S., Oosterhoff, L. A., Vernooij, I. G. W. H., Schrall, I. M., van Wolferen, M. E., Bannink, F., Roesch, C., van Uden, L., Molenaar, M. R., Helms, J. B. et al. Long-term adult feline liver organoid cultures for disease modeling of hepatic steatosis. *Stem Cell Reports*, **2017**, 8(4): 822–830. https://doi.org/10.1016/j.stemcr.2017.02.015

[86] Wan, Z. R., Zhang, H. Y., Zhang, L., Cao, X. F., et al. *JAG1*c.1615C > T mutation impairs bile duct regeneration but not differentiation in hepatic organoids derived from a patient with Alagille syndrome. *Stem Cells Translational Medicine*, **2026**, 15(10): szag073. https://doi.org/10.1093/stcltm/szag073

[87] Roman, G., Lauritzen, K. H., Harrison, S. P., Bhattacharya, A., Andresen, M. S., Mowinckel, M. C., Smolkova, B., Henriksson, C. E., Glosli, H., Iversen, N. et al. *Ex vivo* correction of severe coagulation Factor VII deficiency in patient-derived 3D liver organoids. *Haematologica*, **2025**, 111(3): 941−954. https://doi.org/10.3324/haematol.2025.288046

[88] Louey, A., Hernández, D., Pébay, A., Daniszewski, M. Automation of organoid cultures: Current protocols and applications. *SLAS Discovery*, **2021**, 26(9): 1138–1147. https://doi.org/10.1177/24725552211024547

[89] Jin, Y., Park, S., Cho, S. W. Organoid analytical toolkits. *Nature Reviews Bioengineering*, **2026**, 4(4): 336–352. https://doi.org/10.1038/s44222-025-00384-5

[90] Gough, A., Soto-Gutierrez, A., Vernetti, L., Ebrahimkhani, M. R., Stern, A. M., Taylor, D. L. Human biomimetic liver microphysiology systems in drug development and precision medicine. *Nature Reviews Gastroenterology & Hepatology*, **2021**, 18(4): 252–268. https://doi.org/10.1038/s41575-020-00386-1

[91] Han, X. X., Cai, C. H., Deng, W., Shi, Y. H., Li, L. Y., Wang, C., Zhang, J., Rong, M. J., Liu, J. P., Fang, B. J. et al. Landscape of human organoids: Ideal model in clinics and research. *The Innovation*, **2024**, 5(3): 100620. https://doi.org/10.1016/j.xinn.2024.100620