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Review Article

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Cell-Based Therapies for Liver Disease: From Transplantation to Regenerative and Immuno-Engineered Solutions

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ABSTRACT

Liver disease remains a major global health challenge, with chronic and acute liver failure continuing to drive high morbidity and mortality. The current standard of care for end stage liver disease is allogeneic liver transplantation combined with long term immunosuppressive therapy. Although lifesaving, transplantation is constrained by immune mediated graft rejection, surgical complications including reperfusion injury, off target toxicities of immunosuppressants such as nephrotoxicity, and severe donor organ shortages. These limitations have intensified efforts to develop regenerative strategies that harness the liver's intrinsic repair mechanisms. This review provides an integrated overview of emerging cell-based therapies for liver regeneration, including primary hepatocytes, hepatic progenitor cells, mesenchymal stem cells, and induced pluripotent stem cell derived hepatocytes. We highlight the growing importance of immune cell–based approaches, such as Kupffer cells, dendritic cells, and tolerogenic dendritic cells, which regulate inflammation, promote immune tolerance, and remodel the hepatic microenvironment to support repair. We critically evaluate the strengths, limitations, and translational barriers associated with each cell category, including sourcing, scalability, immunogenicity, and therapeutic durability. Advances in organoid-based liver models and liver like constructs are also discussed, with emphasis on their potential for personalised therapy, immune education, and biobanked regenerative products. This review synthesises current evidence, highlights key challenges, and outlines future directions for integrating cell therapies, immune-modulating strategies, and organoid technologies into clinical practice. Altogether, these regenerative and immuno-engineered innovations might signal a shift away from traditional transplantation toward more precise and functional restoration of the diseased liver.

Keywords: Liver Failure, Alternate to Transplantation, Cell Based Therapies, Stem Cells, Organoids, Tolerogenic Dendritic Cells, Tissue Engineering, Regenerative Medicine

Introduction

Owing to the liver's wide-ranging influence on systemic homeostasis and bodily function, liver failure represents a critical and often life-threatening condition. With an ageing global population and the increasing prevalence of lifestyle-related morbidities, the global burden of liver disease now affects more than 800 million people worldwide, with an associated mortality of approximately two million deaths annually [1-4]. Together, these factors impose substantial economic and social costs, underscoring the urgent need for improved preventative, diagnostic, and therapeutic strategies.

With effective diagnostic approaches and early clinical intervention, many forms of liver injury and disease are preventable or manageable. However, delayed access to care, limited healthcare resources, and incomplete understanding of disease progression frequently result in undiagnosed or untreated liver pathology. In such cases, persistent injury can drive progressive and chronic hepatic deterioration, culminating in cirrhosis, severe hepatic dysfunction, and ultimately, liver failure [5].

The Liver: Structure, Function, and Regenerative Capacity

The liver is the body's primary metabolic organ, responsible for energy homeostasis and the detoxification of harmful endogenous and exogenous compounds. This central metabolic role is supported by highly specialised and coordinated parenchymal and non-parenchymal cell populations (As illustrated in Figure 1). Hepatocytes, the principal parenchymal epithelial cells, comprise approximately two thirds of the liver's total mass and perform the majority of hepatic metabolic functions, including glycogenesis, protein synthesis, bile production, and xenobiotic metabolism. Complementing hepatocytes are biliary epithelial cells, which line the intra- and extra-hepatic bile

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ducts and regulate bile modification and transport [6]. The non-parenchymal compartment includes liver sinusoidal endothelial cells, hepatic stellate cells, and resident immune populations such as Kupffer macrophages, dendritic cells and natural killer cells (As illustrated in Figure 1). Together, these cell types maintain vascular integrity, immune surveillance, extracellular matrix regulation, and tissue homeostasis, underpinning the liver's essential roles in metabolism, hormonal regulation, and waste removal [6].

One of the liver's most remarkable characteristics is its intrinsic regenerative capacity. Following injury or partial hepatectomy, the liver can restore its original mass from as little as a third of its total mass (7). This regenerative response is primarily driven by the proliferative capacity of mature hepatocytes, which re-enter the cell cycle in response to growth factors such as hepatocyte growth factor and cytokines including interleukin-6 [7]. However, dysregulation of this tightly controlled process can result in pathological outcomes, including chronic hepatitis, fibrosis, and, in advanced cases, cirrhosis. These conditions compromise hepatic structure and function and may progress to chronic liver disease, hepatic dysfunction, or failure [8].

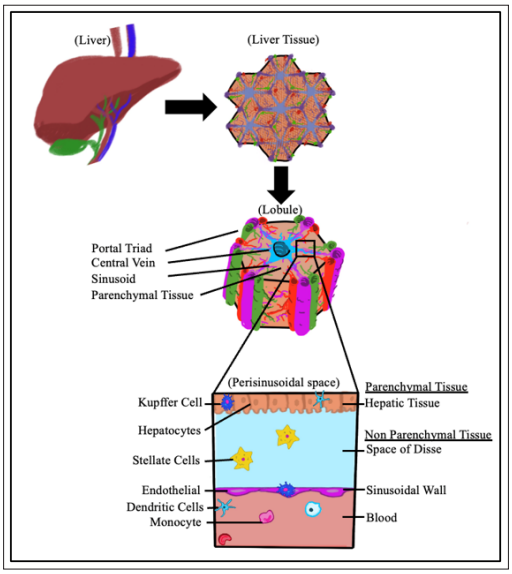

Figure 1: Illustration Describing the Histology and Cellular Composition of the Liver. Adapted from [9].

Chronic and Acute Liver Failure

Chronic liver disease arises from persistent hepatic injury in which sustained immune dysregulation and inflammation overwhelm the liver's intrinsic regenerative capacity. In chronic hepatitis, prolonged activation of hepatic immune populations—including Kupffer cells and cytotoxic and regulatory T lymphocytes—drives persistent cytokine and chemokine signalling, resulting in continuous immune-mediated hepatocellular damage and impaired regenerative responses. When inflammatory injury exceeds reparative potential, progressive hepatocyte loss, necrosis, and fibrotic remodelling ensue, ultimately compromising hepatic architecture and function [10].

Repeated parenchymal injury promotes activation of hepatic stellate cells and fibrogenic macrophages, leading to excessive extracellular matrix deposition and accumulation of activated myofibroblasts. Fibrosis represents an early pathological response to chronic liver injury and is often clinically silent yet potentially reversible during initial stages, highlighting a critical window for antifibrotic and regenerative intervention. In the absence of timely diagnosis and treatment, persistent fibrosis progresses to irreversible cirrhosis [3].

Cirrhosis constitutes the terminal stage of chronic liver disease and is characterised by extensive scarring, architectural distortion, and vascular remodelling. Chronic injury induces sinusoidal endothelial capillarisation, reducing permeability and impairing hepatic microcirculation, thereby increasing intrahepatic resistance and driving portal hypertension. These pathological changes culminate in hepatocellular dysfunction and predispose the liver to decompensation and failure. Decompensated cirrhosis is associated with systemic complications including jaundice, hepatic encephalopathy, coagulopathy, recurrent infections, and multiorgan dysfunction [11].

In contrast, acute liver failure is a rare but rapidly progressive condition characterised by sudden loss of hepatic function in individuals without pre-existing liver disease. It may arise from toxin- or drug-induced injury, viral hepatitis, ischaemic hepatitis, or autoimmune mechanisms. Clinically, acute liver failure is marked by the abrupt onset of jaundice, coagulopathy, and hepatic encephalopathy, often progressing over days to weeks. Despite advances in critical care, mortality rates remain high, approaching 40–50% within the first three months of onset. Prompt diagnosis and intervention are therefore essential, with liver transplantation representing the most effective treatment option in severe cases [12].

Liver Transplantation and Immunosuppression: Current Standards and Limitations

Although liver transplantation has advanced considerably since its early conceptualisation in 1926 [13], including innovations such as split-liver transplantation and improved immunosuppressive regimens, it remains associated with substantial limitations. These include high waiting-list mortality rates, persistent risk of immune-mediated rejection—particularly with extended-criteria donor organs—limited histocompatibility for patients from ethnic minority backgrounds, and long-term graft dysfunction resulting from ischaemia–reperfusion injury and chronic immune-mediated damage [14,15]. In light of these challenges, there is increasing interest in alternative therapeutic strategies capable of improving outcomes and reducing global reliance on transplantation [16].

Current clinical management of liver failure focuses on patient stabilisation, pharmacological intervention, continuous renal replacement therapy, and, where available, liver transplantation. Despite its success, transplantation is associated with rejection rates of approximately 15–25% and persistent shortages of suitable donor grafts and primary human hepatocytes. These limitations contribute to repeat transplantation rates of roughly 10% and the development of cirrhosis in 10–20% of transplant recipients [17,18].

Immunosuppressive therapies are indispensable in modern transplant practice, offering protection against inflammation, chronic hepatitis, and graft rejection [19]. However, excessive immune suppression compromises immune surveillance, increasing susceptibility to opportunistic infections and

malignancies. Consequently, immunosuppressive regimens are often administered alongside antibiotics, which further elevate the risk of complications such as methicillin-resistant Staphylococcus aureus [20]. Many immunosuppressive agents also exert systemic toxicity, particularly nephrotoxicity, adversely affecting recovery and long-term quality of life [21]. Maintaining an optimal balance between immune tolerance and preserved immunological defence therefore remains a central clinical challenge.

Animal Models to Organoids: The Foundations of Regenerative Medicine

To investigate liver biology, disease progression, and therapeutic strategies, researchers have employed a broad spectrum of experimental models, ranging from in vivo animal systems to increasingly sophisticated two- and three-dimensional in vitro platforms [22]. These models have evolved from early embryological studies using avian systems and immortalised cell lines to advanced organoid platforms capable of recapitulating the three-dimensional architecture and developmental processes of hepatic tissue [23-25].

This methodological evolution aligns with the principles of Replacement, Reduction, and Refinement first articulated by Russell and Burch (1959), aiming to minimise animal use while enhancing experimental relevance. Contemporary approaches, including organoids, organ-on-a-chip technologies, and advanced in vitro culture systems, offer improved experimental control and translational potential [26]. In transplantation research, these technologies are increasingly applied to organ preservation, regenerative strategies, and cell-based therapies, with the potential to improve graft viability and clinical outcomes.

From Transplantation to Regeneration: Emerging Paradigms in Liver Therapy

Despite the liver's remarkable regenerative capacity and substantial advances in transplantation surgery and immunosuppressive regimens, liver failure remains a major clinical challenge, with persistently high morbidity and mortality underscoring the need for more effective and durable therapeutic strategies. Recent progress in stem cell-derived therapies and the development of three-dimensional tissue-engineered constructs has catalysed a paradigm shift in regenerative medicine. In parallel, advances in immunomodulatory and organoid-based systems offer the potential to restore hepatic function while reducing healthcare's reliance on organ donation, long-term immunosuppression, and invasive surgical intervention [27]. This review critically examines the evolution, current state, and future direction of liver regenerative strategies, integrating immunotherapy, tissue engineering, and cell-based approaches as emerging alternatives capable of redefining the clinical management of liver disease and failure.

Cell-Based Therapies for Regenerative Medicine

Cell-based regenerative medicine seeks to restore liver structure and function through the delivery of functional cells capable of replacing damaged tissue, modulating endogenous repair pathways, or halting progressive injury. These strategies are frequently positioned as alternatives to orthotopic liver transplantation, which remains constrained by donor organ scarcity, immune rejection, surgical morbidity, and the lifelong requirement for systemic immunosuppression. However, while the liver's intrinsic regenerative capacity and cellular plasticity make it an attractive therapeutic target, these same characteristics underscore the complexity of recapitulating coordinated, zonated hepatic function through exogenous cellular delivery. The translational viability of cell-based interventions therefore remains contingent on overcoming substantial biological and engineering barriers.

Strengths of Cell-Based Regenerative Strategies

Cell-based therapies offer several conceptual and translational advantages. Most notably, they present the possibility of organ repair without whole-organ replacement, theoretically reducing dependence on donor grafts. Advances in stem cell biology cellular reprogramming have enabled the generation of large quantities of liver-relevant cells from diverse sources, suggesting that scalability—historically a major limitation—may become increasingly manageable.

In addition, the clinical success of cell-based interventions in other medical domains provides important proof-of-principle. Induced pluripotent stem cell (iPSC)–derived platelets in clinical trials and FDA-approved CAR-T cell therapies for haematological malignancies demonstrate that highly engineered cellular products can progress from experimental platforms to regulated clinical therapies. These examples substantiate the broader feasibility of translating complex cell-based technologies into practice [28,29].

Nevertheless, extrapolation from these systems to hepatic regeneration warrants caution. Haematological and immune-cell therapies operate within fundamentally different structural and functional contexts than the liver, which requires coordinated metabolic, synthetic, and detoxification activity across a highly organised sinusoidal architecture. Consequently, while these precedents are encouraging, they do not eliminate the unique translational challenges posed by solid-organ regeneration.

Cell Sourcing and Therapeutic Success

The first—and arguably most determinative—step in developing effective cell-based liver therapies is cell sourcing. Approaches to liver regeneration have utilised cells derived directly from hepatic tissue as well as extrahepatic somatic cells enabled by advances in cellular reprogramming, as illustrated in Figure 2 [30]. The choice of cell source has profound implications for engraftment efficiency, phenotypic fidelity, immunogenicity, and long-term therapeutic efficacy.

Hepatic-derived cells may offer greater lineage fidelity but are limited by donor availability and expansion constraints. Conversely, extrahepatic reprogrammed cells provide theoretical scalability yet introduce additional layers of epigenetic instability, maturation inefficiency, and safety uncertainty. Thus, cell sourcing is not merely a logistical consideration but a central biological determinant of regenerative outcome. Careful evaluation of lineage stability, microenvironmental responsiveness, and long-term functional integration will be essential in defining which cellular platforms are genuinely capable of sustaining meaningful hepatic repair.

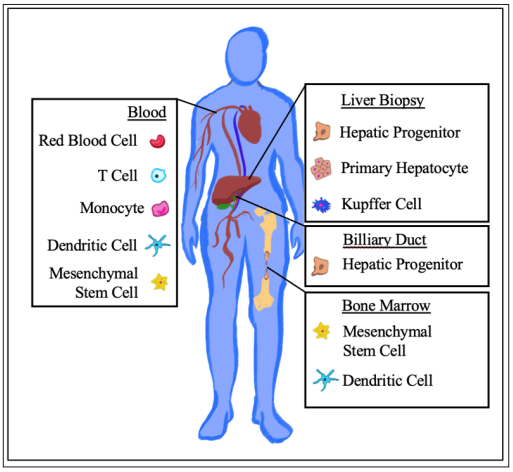

Figure 2: Illustration Describing Examples of Some Cell Types for Regenerative Medicine and Their Varying Sources Throughout the Body. Adapted from [31].

Primary Hepatocytes for Liver regeneration

Primary hepatocytes, from liver biopsies (as illustrated in Figure 2), remain the gold standard for functional liver tissue engineering due to their mature hepatic phenotype. However, their clinical utility is limited by several factors: invasive procurement procedures that may exacerbate liver injury, low in-vitro expansion capacity, and a strong tendency toward dedifferentiation during culture, resulting in loss of hepatic function. Furthermore, hepatocyte availability is particularly restricted in the context of end-stage liver disease, when regenerative therapies are most needed [32].

Consequently, increasing attention has shifted toward non-hepatic somatic cell sources, including hepatic progenitor cells, multipotent stem cells, and pluripotent stem cells. This strategy has shown encouraging progress using hepatic progenitor cells, bone-marrow–derived mesenchymal stem cells, and blood monocytes. While these cells offer advantages in accessibility and expandability, their ability to fully recapitulate mature hepatic function remains an area of active investigation. Each of these cell sources will be examined in detail in subsequent sections, with emphasis on their biological potential, limitations, and translational relevance [33].

Hepatic Progenitor Cells for Liver Regeneration

In addition to mature hepatocytes, hepatic progenitor cells (HPCs), from the billiary duct or liver biopsies (as illustrated in Figure 2), represent a potential cell source for liver regeneration. Under physiological conditions, hepatocytes are the principal mediators of liver regeneration; however, when hepatocyte proliferation is impaired, regeneration can shift toward activation of biliary-derived hepatic progenitor cells, often referred to as a secondary regenerative pathway [34].

HPCs have been isolated from multiple intrahepatic and extrahepatic niches, including bile ducts and periportal regions. Despite this distribution, endogenous hepatic progenitor cells have demonstrated limited hepatocyte repopulation capacity in vivo, consistent with their relatively minor role in parenchymal homeostasis [35]. While these cells exhibit robust proliferative potential, they preferentially contribute to periportal regeneration rather than widespread lobular repopulation, thereby limiting their ability to restore liver mass and function at the organ level. This proliferative capacity nevertheless renders HPCs attractive candidates for ex vivo expansion followed by directed differentiation or lineage reprogramming into hepatocyte-like cells. The conceptual foundation for such reprogramming strategies was established by Shinya Yamanaka in 2007, when defined transcription factors were shown to induce differentiated adult cells into a pluripotent stem-cell-like state [36]. This discovery demonstrated that cellular identity is not fixed but can be actively remodelled, fundamentally reshaping regenerative medicine. Building on this principle, subsequent studies have adapted transcription factor–mediated reprogramming approaches to generate progenitor-like intermediates from various somatic cell types.

For example, recent work by Kang He et al (2025) applied this framework to reprogram primary hepatocytes into hepatocyte-derived liver progenitor cells (HepLPCs) [34]. In a small clinical study, HepLPC transplantation was associated with extracellular matrix remodelling, reduced inflammation, and increased liver volume in six of eight treated patients. These findings suggest that progenitor-like intermediates may enhance regenerative outcomes compared with mature hepatocyte transplantation alone, potentially combining proliferative flexibility with lineage fidelity.

Despite these promising results, the approach described by Kang He et al (2025) remains constrained by the requirement for an initial hepatocyte source and may therefore be more applicable to chronic hepatitis than to end-stage liver failure, where viable hepatocytes are scarce [34]. Alternative progenitor sources, including biliary epithelial cells and fibrotic stromal cells, have consequently been investigated. Biliary Tree Stem cells offer a physiologically relevant progenitor population, although their limited accessibility in adults and restricted expansion capacity may constrain clinical scalability [37]. In contrast, fibrotic cells—abundant within cirrhotic livers—represent a more readily available and potentially autologous starting population.

Supporting this strategy, Kai Liu et al (2025) demonstrated in murine models that fibroblast-derived hepatic progenitor cells can be generated through lentiviral genetic editing, resulting in functional hepatocyte repopulation with anti-inflammatory therapeutic effects [38]. Advances in trans-differentiation and direct reprogramming approaches have therefore expanded the therapeutic landscape of hepatic progenitor cells, positioning them as adaptable, though still technically demanding, candidates for future regenerative interventions in liver disease [39].

Bone Marrow Mesenchymal Stem Cells for Liver Regeneration

Mesenchymal stem/stromal cells (MSCs), from Bone Marrow (as illustrated in Figure 2), represent another widely investigated extrahepatic cell source for liver regeneration due to their inherent regenerative roles, accessibility, expansion capacity, and potent immunomodulatory effects [40]. MSCs are most commonly isolated from bone marrow and adipose tissue, although additional sources include umbilical cord and placental tissue. Unlike lineage-restricted hepatic progenitors or pluripotent stem cells, MSCs contribute to liver repair predominantly through paracrine and microenvironmental mechanisms, rather than direct replacement of hepatocytes.

Early studies demonstrated that bone marrow–derived MSCs possess the capacity to transdifferentiate into hepatocyte-like cells under specific in vitro and in vivo conditions [41]. However, subsequent work has shown that stable engraftment and functional hepatocyte replacement are rare, with therapeutic benefits largely mediated through indirect mechanisms. These include secretion of trophic factors, modulation of inflammatory signalling, attenuation of fibrosis, and promotion of angiogenesis [42].

A defining feature of MSC-based therapies is their immunoregulatory capacity. MSCs secrete anti-inflammatory cytokines such as IL-10 and TGF-β, inhibit T-cell proliferation, and promote macrophage polarisation toward reparative phenotypes (42). In chronic liver disease, where sustained inflammation drives fibrosis and parenchymal loss, these properties enable MSCs to stabilise the hepatic microenvironment and support endogenous regenerative processes.

Beyond immune regulation, MSCs also contribute to non-parenchymal tissue repair, including restoration of the hepatic vasculature. Through secretion of pro-angiogenic factors such as vascular endothelial growth factor (VEGF), MSCs support perivascular cell function, sinusoidal repair, and extracellular matrix remodelling [43]. This vascular support is clinically significant, as preservation of sinusoidal and portal architecture is essential for hepatocyte survival and metabolic function following injury.

Despite these advantages, MSC-based therapies face important biological and translational limitations. Differentiation into mature, fully functional hepatocytes remains inefficient, and observed therapeutic effects are often transient [41]. In addition, MSC populations are inherently heterogeneous, with donor source, culture conditions, and inflammatory context significantly influencing their secretory profile and regenerative efficacy [40].

Critically, MSC behaviour is highly microenvironment dependent. While MSCs can exert anti-inflammatory and antifibrotic effects in chronically injured liver, evidence suggests that under certain conditions they may adopt a myofibroblast-like phenotype, expressing markers such as α-smooth muscle actin and vimentin, thereby potentially exacerbating fibrosis. Their migratory capacity also raises safety concerns regarding unintended incorporation into tumour stroma, where MSC-derived fibroblast-like cells may promote angiogenesis, immune evasion, and tumour progression [44].

Consequently, MSCs are best viewed not as direct replacements for lost hepatic parenchyma, but as biological modulators of the regenerative niche, acting primarily through paracrine signalling, immune regulation, and vascular support [42]. Emerging strategies such as inflammatory priming or the use of MSC-derived extracellular vesicles and exosomes may improve therapeutic consistency while mitigating context-dependent risks, reinforcing the role of MSCs in shaping the hepatic microenvironment rather than directly repopulating hepatocytes.

iPSC Cell Therapies for Liver Regeneration

Induced pluripotent stem cell (iPSC)–derived therapies have attracted substantial interest in regenerative medicine due to their theoretically unlimited expansion capacity and pluripotent potential to generate patient-specific, autologous cell populations. iPSCs can be generated from a range of accessible somatic tissues, including blood monocytes (as illustrated in Figure 2), skin biopsies, hair follicles, kidney epithelial cells, and primary liver or biliary samples [25]. Although their derivation and differentiation present functional, immunogenic, and manufacturing challenges, iPSCs offer the unique capacity to generate both parenchymal and non-parenchymal hepatic cell populations, enabling the construction of increasingly complex and self-organising tissue models.

iPSCs are produced by reprogramming somatic cells into a pluripotent state, typically through the introduction of defined transcription factors—most commonly the Yamanaka factors Oct4, Sox2, Klf4, and c-Myc—which revert mature cells to an embryonic stem cell–like phenotype [27,36,45]. This reprogramming paradigm demonstrated that cellular identity is epigenetically plastic and can be experimentally remodelled, establishing the conceptual foundation for patient-specific regenerative platforms.

The success of iPSC-based hepatic differentiation has relied heavily on insights from developmental biology. Liver organoid technology, for example, draws directly from knowledge of liver organogenesis, particularly the emergence of hepatoblasts from the posterior foregut endoderm. During embryogenesis, mesenchymal cues—including FGF, BMP, HGF, and Wnt signalling—govern hepatoblast proliferation, migration, and lineage commitment. By recapitulating these developmental pathways ex vivo, researchers can direct iPSCs toward hepatocyte, cholangiocyte, or mixed hepatic lineages with increasing fidelity [25].

Eugenia Pareja et al (2020) demonstrates this approach by reprogramming skin fibroblasts via transcription factor–mediated retroviral gene delivery and subsequently differentiating the resulting iPSCs into hepatocyte-like cells through multistep growth factor–guided protocols [46]. They further proposed that large-scale bioreactor systems could help overcome production bottlenecks, enabling clinically relevant cell yields. The development of iPSC-derived hepatocyte-like cell biobanks has likewise been suggested as a strategy to provide readily available cellular grafts for liver failure, potentially decoupling therapeutic availability from donor organ constraints [46].

Despite these advances, iPSC-based therapies remain constrained by substantial biological and translational challenges. Reprogramming and directed differentiation are complex, multistage processes that are labour-intensive, time-consuming, and costly. Rigorous quality control is essential, as iPSCs may harbour genetic instability, retain epigenetic memory from their tissue of origin, or exhibit incomplete differentiation—all of which increase the risk of tumorigenicity or functional immaturity [46]. Furthermore, hepatocyte-like cells derived from iPSCs frequently display foetal-like metabolic profiles rather than full adult hepatic functionality, raising questions about their long-term therapeutic equivalence.

The extrahepatic origin of many starting cell populations introduces additional lineage-specification challenges, requiring

tightly controlled signalling environments to ensure stable hepatic fate commitment. Extensive molecular and functional characterisation is therefore necessary before clinical application. Collectively, these constraints highlight that while iPSC platforms offer unparalleled scalability and cellular versatility, their safe and durable translation into liver regenerative therapies depends on continued optimisation of reprogramming efficiency, maturation fidelity, manufacturing scalability, and safety-enhanced differentiation protocols [46].

Immune Cells for Liver Regeneration

Hepatocyte repopulation represents only one component of liver regeneration. Evidence from mesenchymal stem cell studies and observations in chronic inflammatory liver disease indicate that immune modulation is equally central to regenerative outcomes [42,47]. The liver is an immunologically specialised organ in which resident and infiltrating immune populations coordinate the balance between tissue repair and fibrogenesis. Immune cells can be found throughout the body (as illustrated in Figure 2) and in very high abundance in the Liver, where they secrete cytokines, chemokines, and growth factors that can initiate, propagate, or terminate regenerative responses, underscoring their regulatory influence over hepatic homeostasis.

Kupffer Cells in Liver Regeneration

Kupffer cells, the resident macrophages of the liver, account for approximately 90% of the body's resident macrophage population and were among the first immune cell types implicated in regenerative signalling [48]. During the priming phase of liver regeneration, Kupffer cells secrete cytokines such as TNF-α and IL-6, which promote hepatocyte cell-cycle entry and enable progression from quiescence to proliferation. Beyond their role in endogenous regeneration, Zheng et al. (2023) highlight the potential application of Kupffer cells in inducing a tolerogenic microenvironment to support transplantation and graft survival [48].

However, macrophage activity is highly context-dependent, and much of the existing literature remains focused on mechanistic characterisation rather than translational exploitation. While their contribution to cytokine-mediated priming and immune modulation is well described, comparatively few studies have rigorously evaluated their direct therapeutic application or their capacity to modulate graft rejection in vivo. This translational gap limits current understanding of how Kupffer cell–based strategies might be harnessed clinically [48].

In contrast, other immune populations—particularly dendritic cells—have undergone more substantial clinical development within immunology and regenerative medicine, reflecting a broader shift toward targeted immune modulation rather than reliance on resident macrophage biology alone.

The Therapeutic Potential of Dendritic Cells

Dendritic cells (DCs) are a widely distributed population of professional antigen-presenting cells (APCs) that play a central role in immune surveillance and regulation. They initiate and shape adaptive immune responses through antigen processing and presentation to T cells, thereby directing downstream cytokine production and inflammatory activation [49]. DCs are uniquely positioned at the interface of innate and adaptive immunity, with the capacity to present endogenous antigens via MHC class I and exogenous antigens via MHC class II pathways. This dual presentation capacity, combined with their ability to promote either immune activation or immune tolerance, underscores their functional plasticity [50].

Because of this dynamic regulatory capacity, dendritic cells have emerged as attractive targets for therapeutic manipulation in contexts where immune modulation is desirable, including transplantation and autoimmune disease. Rather than functioning solely as immune activators, DCs can be conditioned to suppress pathological immune responses, effectively acting as a cellular immunomodulatory therapy.

To generate immunosuppressive dendritic cells—commonly termed tolerogenic dendritic cells (TolDCs)—a variety of cells, primarily from blood, and in vitro conditioning strategies have been developed. DC's can be obtained from blood monocytes, bone marrow stem cells and peripheral blood mononuclear cells [51]. These approaches utilise defined cytokines, growth factors, or pharmacological agents to induce stable alterations in surface co-stimulatory molecule expression, cytokine secretion profiles, and metabolic programming [52]. However, establishing and maintaining a truly tolerogenic phenotype remains technically challenging. Functional validation typically relies on flow cytometric assessment of co-stimulatory and inhibitory surface markers, in vitro immune suppression assays, and metabolic or cytokine profiling to confirm regulatory activity. Ensuring phenotypic stability following in vivo administration remains an unresolved translational question.

Tolerogenic Dendritic Cells: A Cell-Based Immunotherapy

Tolerogenic dendritic cells (TolDCs) represent a specialised application of dendritic cell plasticity for therapeutic immune modulation in liver disease and transplantation [53]. Under tolerogenic conditioning, with compounds like dexamethasone or activated vitamin D3, DCs exhibit an immature phenotype, with a reduced expression of co-stimulatory molecules, diminished effector T-cell priming capacity, enhanced induction of regulatory T cells, and increased secretion of anti-inflammatory mediators. Through these coordinated changes, TolDCs aim to recalibrate immune balance rather than induce broad systemic immunosuppression [54].

Monocyte-derived dendritic cells, owing to their relative abundance and accessibility, have emerged as a practical source for TolDC generation [51]. Conditioning with granulocyte–macrophage colony-stimulating factor and interleukin-4 enables differentiation, while additional exposure to anti-inflammatory cytokines such as interleukin-10 promotes acquisition of a tolerogenic phenotype. In murine models, IL-10–pulsed TolDCs have demonstrated reduced T-cell activation, modulation of T-cell apoptosis, anergy, and hypo-responsiveness, and prolonged xenograft survival [51]. These findings provide proof-of-concept that TolDC-based strategies can influence immune dynamics in ways supportive of graft tolerance and hepatic repair.

However, translation beyond preclinical systems remains uncertain. The in vivo stability of the tolerogenic phenotype, resistance to inflammatory reprogramming, scalability under clinical manufacturing standards, and optimisation of

administration strategies remain incompletely defined [55,56]. The hepatic immune microenvironment—characterised by constant antigen exposure and intrinsic tolerogenic bias—may either support or unpredictably reshape infused TolDCs, a variable not fully recapitulated in experimental models.

The implementation of TolDC therapy therefore requires rigorous evaluation of both short-term immunomodulatory effects and long-term immune consequences. Although conventional pharmacologic immunosuppressants can be titrated and combined to manage adverse effects, they impose systemic toxicities that constrain their therapeutic window. TolDCs offer a theoretically more targeted alternative; nevertheless, they remain subject to the same fundamental risk spectrum of over- or under-immunosuppression. Excessive or prolonged tolerogenic activity could impair host defence, increasing susceptibility to infection, malignancy, metabolic disturbance, cardiovascular complications, and renal dysfunction. Chronic kidney disease develops in approximately 20% of liver transplant recipients within five years, largely due to prolonged systemic immunosuppression. Conversely, insufficient immune modulation may permit inflammatory activation that jeopardises graft survival and contributes to chronic hepatitis, fibrosis progression, or rejection [57].

A central unresolved challenge lies in defining optimal dosing paradigms and delivery schedules—whether single or repeated infusions are required to achieve durable yet controlled immune recalibration [56]. As with pharmacologic regimens, TolDC-based approaches must achieve a precise equilibrium between immune tolerance and immune competence. Their activity should ideally be spatially restricted to the hepatic environment to minimise systemic spillover while preserving protective immunological surveillance [10].

Ultimately, the clinical viability of TolDC therapy will depend on demonstrating controlled localisation, phenotypic stability, predictable persistence, and reproducible manufacturing at scale. Without these safeguards, TolDCs risk replicating—rather than resolving—the systemic vulnerabilities associated with conventional immunosuppression.

Limitations and Challenges of Cell-Based Therapies

Despite their theoretical promise, significant challenges continue to limit the clinical impact of cell-based liver therapies. Many candidate cell populations demonstrate restricted in-vitro proliferative capacity or phenotypic instability during prolonged culture, compromising functional fidelity at the point of transplantation. Even where expansion is technically feasible, maintaining lineage specification and metabolic competence remains difficult [46].

Manufacturing constraints further complicate translation. High production costs, stringent Good Manufacturing Practice requirements, and batch-to-batch variability pose substantial barriers to scalability and equitable clinical deployment [55]. Moreover, the long-term safety, engraftment behaviour, and functional stability of bioengineered or reprogrammed cells in vivo remain incompletely characterised. Risks of aberrant differentiation, maladaptive remodelling, immune activation, or oncogenic transformation cannot be dismissed without comprehensive longitudinal data. These limitations substantially restrict widespread clinical adoption and underscore that cell-based liver regeneration remains, at present, an evolving rather than established therapeutic paradigm.

To overcome these limitations, researchers have sought to increase the biomimetic complexity of their models. This comes as two-dimensional cell cultures, which is biomimetically removed from three dimension in-vivo tissue environments, lack the model complexity and organisation that is conducive of in-vivo tissue behaviours, primarily showing insights only into molecular interactions. A new generation of three dimensional complex cell models, with emerging therapeutic potential, known as organoids show promise in overcoming these limitations in cell-based liver therapy [58].

Organoid Based Therapy: The Future of Regenerative Medicine

Organoids are self-organising 3D tissues that can be derived from ex-vivo biopsies or somatic cells like Hepatocytes, HPSC, iPSC's or Mesenchymal Stem Cells for instance [59]. They represent another promising future for bench to bedside regenerative medicine. They serve not only as cutting-edge experimental models but also as a potential strategy for cultivating 3D hepatic tissue for transplantation. The self-organising heterogeneous populations of parenchymal and non-parenchymal cells in liver organoids (as illustrated in Figure 3), allow them to form complex histoarchitectural features that have been able to closely mimic the liver's native structures and functions [8]. This capacity makes organoid technology a compelling platform for advancing cell-based regenerative therapies and providing a scalable alternative to allografts and organ transplantation.

Liver-Like Organoid Generation Strategies

A wide range of methodologies has been developed to generate both iPSC- and mesenchymal stem cell-derived liver-like organoids, primarily aimed at improving upon conventional two-dimensional culture systems by introducing three-dimensional architecture and multicellular complexity. Current strategies attempt to optimise multiple parameters simultaneously, including biomaterial composition, extracellular matrix (ECM) engineering, micropatterning, growth factor staging, cellular heterogeneity, organotypic structural organisation, bioreactor integration, microfluidic perfusion, and scalability. Despite substantial progress, many reported liver-like organoids remain costly to produce and display limited metabolic maturity relative to adult hepatocytes [59].

Early-generation hepatic organoids largely prioritised hepatocyte-lineage specification. While these models successfully generated hepatic populations capable of albumin secretion and limited cytochrome activity, their metabolic functionality and architectural fidelity frequently resembled foetal rather than adult liver tissue [59]. This functional immaturity remains a persistent barrier to translational application.

More recent protocols have sought to address these shortcomings through improved self-organisation and vascularisation. Harrison et al. (2023) described a reproducible 20-day protocol for generating liver-like organoids from human pluripotent stem cells, including both embryonic and induced pluripotent lines [60]. Their approach utilised initial single-cell dissociation

followed by aggregation in shaking suspension culture with ROCK inhibition to promote survival and self-assembly. Differentiation was staged through sequential induction of primitive streak and definitive endoderm, hepatic endoderm specification, and maturation using defined media formulations and small-molecule modulation. Notably, these organoids demonstrated vascular-like structures, suggesting partial recapitulation of intrahepatic endothelial development.

The capacity for vascularisation represents an important conceptual advance, as perfusion and endothelial signalling are critical determinants of hepatic maturation and zonal patterning. Furthermore, the potential for anastomosis following transplantation introduces translational relevance. However, despite these advances, limitations remain evident. Scalability, incomplete recreation of hepatic zonation gradients, restricted non-parenchymal diversity, and uncertain long-term functional stability continue to constrain therapeutic applicability. Vascular structures formed in vitro do not necessarily equate to functional haemodynamic integration in vivo.

Parallel efforts have focused on increasing cellular diversity to more faithfully reproduce hepatic microarchitecture. Hyo Jin Kim et al. (2023) generated multilineage liver organoids (mLOs) by differentiating human pluripotent stem cells into hepatic endoderm cells, endothelial cells, and hepatic stellate cell–like populations, which were subsequently recombined in defined ratios [61]. These cells were aggregated in ultra-low attachment conditions using a multilineage medium containing a complex combination of growth factors and pathway modulators, including BMP7, FGF19, HGF, VEGF, TGF-β inhibition (A83-01), Notch inhibition (DAPT), and low-concentration Matrigel support. Organoids were matured in staged conditions with optimisation of cell-type ratios to promote structural organisation.

These multilineage constructs demonstrated vascularisation, bile duct–like structures, and the formation of relatively large organoids without necrotic cores [61]. The intentional incorporation of parenchymal, vascular, and mesenchymal compartments (as illustrated in Figure 3) marks a significant departure from hepatocyte-dominant systems and better reflects the multicellular interdependence of native liver tissue. However, even these advanced models remain simplified relative to the in vivo liver, lacking full immune integration, physiologic oxygen gradients, sinusoidal shear stress, and true lobular zonation. The absence of these spatial and mechanical cues limits their ability to model metabolic compartmentalisation and long-term regenerative dynamics.

Collectively, these studies illustrate meaningful progress in liver organoid engineering. Advances in multicellular assembly, vascularisation, toxin metabolism, and disease modelling suggest that increasingly sophisticated platforms are emerging. Nevertheless, the field remains constrained by persistent challenges in scalability, reproducibility, metabolic maturation, and functional integration. While liver-like organoids provide powerful experimental systems and hold promise for regenerative applications, their translation toward clinically viable grafts will require further refinement of architectural precision, perfusion strategies, and in vivo engraftment capacity [27].

Tolerogenic Organoids

Tolerogenic DC's also offer another promising application in a tolerogenic phenotype or state in tissue and organs before transplantation [62]. This unique capability could also be expanded to other cell treatments, for example the conditioning of organoids for allogenic transplantation. Introducing tolerogenic dendritic cells into organoid cultures exposes the emerging tissue to regulatory signals that suppress pro-inflammatory pathways and promote immune tolerance, including more controlled and compatible antigen presentation. Through this interaction, organoids may acquire a tolerogenic phenotype characterized by reduced activation of alloreactive immune responses following transplantation. This could be used to not only prevent rejection of allogenic organoids but also mitigate the inflammatory response present in acute liver failure, allowing the organoid and liver to both integrate and regenerate without complications from conditions like chronic hepatitis.

Tolerogenic organoids may be generated through several complementary strategies. One approach involves the direct incorporation of tolerogenic dendritic cells (TolDCs) into the organoid system as a composite therapeutic construct. This strategy offers the potential to actively promote a local tolerogenic microenvironment; however, the long-term stability and in vivo behaviour of TolDCs remain poorly characterised raising concerns about their long term effectiveness and behaviours [63].

An alternative strategy is the transient incorporation of dendritic cells during organoid culture to induce a tolerogenic phenotype prior to implantation (as illustrated in Figure 3), followed by maturation on a three-dimensional scaffold. While this approach may limit the duration of immune modulation after transplantation, it offers a potentially safer long-term profile by reducing prolonged immune suppression in vivo. Together, these strategies highlight a trade-off between durable local tolerance and long-term safety, underscoring the need for careful optimisation and in vivo validation.

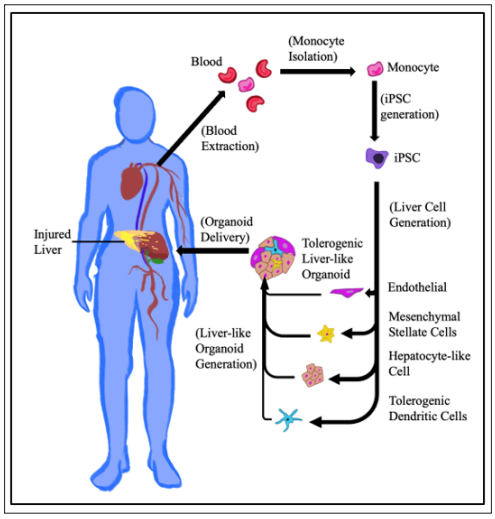

Figure 3: Illustration Describing the Autologous Therapeutic Potential of Blood-Monocyte iPSC Derived Tolerogenic Organoids in Treating Liver Failure.

Biobanks and the Future of Regenerative Medicine

iPSC-derived stem cell therapies, tolerogenic dendritic cell strategies, and liver organoids collectively represent a potentially

scalable alternative to conventional liver transplantation and long-term systemic immunosuppression. By integrating cell-based regenerative platforms with immune-conditioning strategies and cryopreservation technologies, it may become possible to develop partially standardised, distributable graft products. Such approaches aim to reduce dependence on strict donor–recipient matching while preserving functional engraftment capacity, thereby expanding therapeutic accessibility beyond the constraints of traditional allogeneic organ transplantation [64].

This paradigm introduces the concept of regenerative biobanks: repositories in which tissue derived from a limited number of donors could be cryopreserved, quality-controlled, expanded on demand, and distributed to multiple recipients. In contrast to whole-organ transplantation, therapeutic availability would be governed primarily by manufacturing throughput, storage infrastructure, and logistical coordination rather than donor scarcity, geographic inequities, or underrepresentation within minority donor pools. If successfully implemented, such systems could reframe liver replacement from a donor-limited intervention to a production-limited biomedical service.

Clinically, this model could offer rapid intervention for patients with acute liver failure or progressive decompensation who cannot await autologous organoid generation or prolonged transplant waiting times. Combining conventional HLA matching with targeted tolerogenic conditioning strategies may enhance engraftment while potentially reducing reliance on systemic immunosuppression. Cryopreserved organoids could, in principle, be thawed, expanded, and prepared for transplantation in a controlled and time-sensitive manner, introducing greater predictability into treatment timelines.

However, this framework remains largely conceptual and faces substantial translational barriers. First, tolerogenic or partially HLA-matched organoids must demonstrate durable functional integration and stable immune acceptance in both advanced in vitro systems and clinically relevant in vivo models. Immune modulation may reduce rejection risk but is unlikely to eliminate alloimmune surveillance entirely, particularly in long-term settings. Second, cryopreservation protocols must preserve not only cellular viability but also multicellular architecture, vascular integrity, and post-thaw metabolic competence—parameters that remain difficult to standardise across large-scale batches. Third, the long-term safety profile of implanted organoids requires rigorous evaluation, including risks of aberrant proliferation, incomplete differentiation, immune escape, genomic instability, or malignant transformation. Finally, scalable Good Manufacturing Practice (GMP)-compliant production, batch reproducibility, and cost containment will be critical determinants of regulatory approval and equitable access.

Beyond technical feasibility, economic and infrastructural considerations will shape real-world implementation. Manufacturing-intensive regenerative products may reduce donor scarcity yet introduce new bottlenecks in production capacity, distribution networks, and quality assurance oversight. Consequently, while organoid biobanking represents a compelling shift from donor-dependent transplantation toward manufacturable regenerative grafts, its clinical viability will depend on resolving immunological, engineering, regulatory, and economic challenges with the same rigor that underpins contemporary transplant medicine.

Conclusion

Cell-based regenerative medicine represents a transformative frontier in the treatment of liver disease, offering alternatives to orthotopic transplantation that may alleviate donor scarcity, surgical morbidity, and lifelong systemic immunosuppression. Across the spectrum of investigated cell sources—including primary hepatocytes, hepatic progenitor cells, mesenchymal stem cells (MSCs), induced pluripotent stem cells (iPSCs), immune-modulatory dendritic cells, and complex liver organoids—distinct biological strengths are counterbalanced by equally distinct translational constraints.

Primary hepatocytes remain the functional benchmark yet are fundamentally limited by availability and poor expandability. Hepatic progenitor cells introduce proliferative flexibility but have not consistently demonstrated robust large-scale parenchymal repopulation in vivo. MSCs exert meaningful immunomodulatory and microenvironmental effects, although their regenerative contribution is largely indirect and context dependent. iPSC-derived platforms offer scalability and autologous potential but demand precise lineage control and stringent safety validation to mitigate instability and tumorigenicity.

Parallel advances in immune engineering—particularly tolerogenic dendritic cells—underscore that durable regeneration depends as much on immunological equilibrium as on hepatocyte replacement. In this context, liver organoids represent the most integrative platform, combining multicellular architecture with developmental self-organisation. Continued progress in vascularisation, multicellular assembly, and immune conditioning strategies, including tolerogenic organoid design, suggests a trajectory toward more physiologically coherent grafts. The prospect of organoid biobanks introduces a logistical paradigm shift, potentially decoupling transplantation from immediate donor availability.

The central challenge moving forward is not merely generating hepatocyte-like cells, but achieving coordinated control over cellular identity, spatial organisation, vascular integration, and immune compatibility at scale. Liver regeneration is increasingly understood as a systems-level engineering problem rather than a single-cell replacement task. Durable and clinically meaningful repair will require convergence across developmental biology, biomaterials science, immunology, and translational manufacturing frameworks.

The future of liver regenerative medicine will therefore depend less on identifying a singular optimal cell type and more on integrating cellular, architectural, and immunological design principles into cohesive therapeutic systems.

References

1. Kim IH, Kisseleva T, Brenner DA. Aging and liver disease. Curr Opin Gastroenterol. 2015. 31: 184-191.
2. Williams R, Aspinall R, Bellis M, Camps-Walsh G, Cramp M, Dhawan A, et al. Addressing liver disease in the UK: a blueprint for attaining excellence in health care and reducing premature mortality from lifestyle issues of excess

consumption of alcohol, obesity, and viral hepatitis. Lancet Lond Engl. 2014. 384: 1953-1997.
3. Parola M, Pinzani M. Liver fibrosis: Pathophysiology, pathogenetic targets and clinical issues. Mol Aspects Med. 2019. 65: 37-55.
4. Gan C, Yuan Y, Shen H, Gao J, Kong X, et al. Liver diseases: epidemiology, causes, trends and predictions. Signal Transduct Target Ther. 2025. 10: 33.
5. Wazir H, Abid M, Essani B, Saeed H, Khan MA, Nasrullah FNU, et al. Diagnosis and Treatment of Liver Disease: Current Trends and Future Directions. Cureus. 2023. 15: e49920.
6. Horisawa K, Suzuki A. Cell-Based Regenerative Therapy for Liver Disease. Innov Med. 2015. 327-339.
7. Michalopoulos GK, Bhushan B. Liver regeneration: biological and pathological mechanisms and implications. Nat Rev Gastroenterol Hepatol. 2020. 18: 1-16.
8. Gong J, Tu W, Liu J, Tian D. Hepatocytes: A key role in Liver inflammaiton. 2023. 13:1083780.
9. Carter JK, Friedman SL. Hepatic Stellate Cell-Immune Interactions in NASH. Front Endocrinol. 2022. 13: 867940.
10. Panackel C, Mathew JF, Fawas N M, Jacob M. Immunosuppressive Drugs in Liver Transplant: An Insight. 2022. 12: 1557-1571.
11. Engelmann C, Clària J, Szabo G, Bosch J, Bernardi M. Pathophysiology of decompensated cirrhosis: Portal hypertension, circulatory dysfunction, inflammation, metabolism and mitochondrial dysfunction. J Hepatol. 2021. 75: S49-66.
12. Weiler N, Schlotmann A, Schnitzbauer AA, Zeuzem S, Welker MW. The Epidemiology of Acute Liver Failure. 2020. 117: 43-50.
13. Brenner DA. Thomas E. Starzl: Transplantation pioneer. Proc Natl Acad Sci. 2017. 114: 10808-10809.
14. Khalil A, Quaglia A, Gélat P, Nader Saffari, Rashidi H, Davidson BR. New Developments and Challenges in Liver Transplantation. J Clin Med. 2023. 12: 5586-5586.
15. Fernandez J, Octavi Bassegoda, Toapanta D, Bernal W. Acute Liver Failure: A Practical Update. JHEP Rep. 2024. 6: 101131-101131.
16. Sun K, Xie X, Xie J, Jiao S, Chen X, Zhao X, et al. Cell-based therapy for acute and chronic liver failures: Distinct diseases, different choices. 2024. 4: 6494.
17. Likhitsup A, Fontana RJ. Indications and Outcomes with Liver Retransplantation in 2025. Dig Dis Sci. 2024. 70: 29-38.
18. Qazi Arisar FA, Varghese R, Chen S, Xu W, Selzner M, et al. Trajectories of patients relisted for liver transplantation. Ann Hepatol. 2024. 29: 101168.
19. Wiesner RH, Fung JJ. Present state of immunosuppressive therapy in liver transplant recipients. Liver Transpl. 2011. 17: S1-9.
20. Kim YJ, Kim SI, Choi JY, Yoon SK, You YK, Kim DG. Clinical significance of methicillin-resistant Staphylococcus aureus and vancomycin-resistant enterococci colonization in liver transplant recipients. Korean J Intern Med. 2015. 30: 694-704.
21. de Mattos AM, Olyaei AJ, Bennett WM. Nephrotoxicity of immunosuppressive drugs: Long-term consequences and challenges for the future. Am J Kidney Dis. 2000. 35: 333-346.
22. Urzì O, Gasparro R, Costanzo E, De Luca A, Giavaresi G, Fontana S, et al. Three-Dimensional Cell Cultures: The Bridge between In Vitro and In Vivo Models. Int J Mol Sci. 2023. 24: 12046-12046.
23. Kaplan-Arabaci O, Dančišinová Z, Paulsen RE. The Chicken Embryo: An Alternative Animal Model in Development, Disease and Pharmacological Treatment. Pharmacol Res Perspect. 2025. 13: 2.
24. Chalak M, Hesaraki M, Mirbahari SN, Yeganeh M, Abdi S, et al. Cell Immortality: In Vitro Effective Techniques to Achieve and Investigate Its Applications and Challenges. Life. 2024. 14: 417-417.
25. Afonso MB, Marques V, van Mil SWC, Rodrigues CMP. Human liver organoids: From generation to applications. Hepatol Baltim Md. 2023. 79: 1432-1451.
26. Han DW, Xu K, Jin ZL, Xu YN, Li YH, et al. Customized liver organoids as an advanced in vitro modelling and drug discovery platform for non-alcoholic fatty liver diseases. Int J Biol Sci. 2023.19: 3595-3613.
27. Liu S, Cheng C, Zhu L, Zhao T, Wang Z, Yi X, et al. Liver organoids: updates on generation strategies and biomedical applications. Stem Cell Res Ther. 2024. 15: 1.
28. Karagiannis P, Nakauchi A, Yamanaka S. Bringing Induced Pluripotent Stem Cell Technology to the Bedside. JMA J. 2018. 1: 6-14.
29. Mitra A, Barua A, Huang L, Ganguly S, Feng Q, He B. From bench to bedside: the history and progress of CAR T cell therapy. Front Immunol. 2023. 14: 1188049.
30. Srivastava D, DeWitt N. In Vivo Cellular Reprogramming: The Next Generation. Cell. 2016. 166: 1386-1396.
31. Elbourne S. British Journal of Nursing. Cell and body tissue physiology. 2022. https://www.britishjournalofnursing.com/content/clinical-pathophysiology/cell-and-body-tissue-physiology.
32. Sanal MG. Cell therapy from bench to bedside: Hepatocytes from fibroblasts - the truth and myth of transdifferentiation. World J Gastroenterol. 2015. 21: 6427.
33. Liu W hui, Ren L na, Wang T, Nalu Navarro-Alvarez, Tang L jun. The Involving Roles of Intrahepatic and Extrahepatic Stem/Progenitor Cells (SPCs) to Liver Regeneration. Int J Biol Sci. 2016. 12: 954-963.
34. He K, Zhu XJ, Shi YP, Huang WJ, Yang TH, et al. Treatment of liver cirrhosis using hepatocyte-derived liver progenitor-like cells: a prospective, open-label, single-arm, safety trial. Cell Discov. 2025. 11: 88-88.
35. Lanzoni G, Cardinale V, Carpino G. The hepatic, biliary, and pancreatic network of stem/progenitor cell niches in humans: A new reference frame for disease and regeneration. Stem Cells Int. 2016. 64: 277-286.
36. Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, et al. Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors. Cell. 2007. 131: 861-872.
37. Cardinale V, Lanthier N, Baptista PM, Carpino G, Carnevale G, et al. Cell transplantation-based regenerative medicine in liver diseases. Stem Cell Rep. 2023. 18: 1555-1572.
38. Liu K, Li L, He Y, Zhang S, You H, Wang P. Hepatic progenitor cells reprogrammed from mouse fibroblasts repopulate hepatocytes in Wilson's disease mice. Stem Cell

Res Ther. 2025. 16: 1.
39. Wang J, Sun M, Liu W, Li Y, Li M. Stem Cell-Based Therapies for Liver Diseases: An Overview and Update. Tissue Eng Regen Med. 2019. 16: 107-118.
40. Chapel A, Bertho JM, Bensidhoum M, Fouillard L, Young RG, et al. Mesenchymal stem cells home to injured tissues when co-infused with hematopoietic cells to treat a radiation-induced multi-organ failure syndrome. J Gene Med. 2003. 5: 1028-1038.
41. Schwartz RE, Reyes M, Koodie L, Jiang Y, Blackstad M, et al. Multipotent adult progenitor cells from bone marrow differentiate into functional hepatocyte-like cells. J Clin Invest. 2002. 109: 1291-302.
42. Eom YW, Kang SH, Kim MY, Lee JI, Baik SK. Mesenchymal stem cells to treat liver diseases. Ann Transl Med. 2020. 8: 563.
43. Choi S, Jeong J. Mesenchymal Stromal/Stem Cell-Based Therapies for Liver Regeneration: Current Status and Future Directions. Int J Mol Sci. 2026. 27: 619.
44. Li M, Luan F, Zhao Y, Hao H, Zhou Y, et al. Epithelial-mesenchymal transition: An emerging target in tissue fibrosis. Exp Biol Med. 2015. 241: 1-13.
45. Liu X, Huang J, Chen T, Wang Y, Xin S, et al. Yamanaka factors critically regulate the developmental signaling network in mouse embryonic stem cells. Cell Res. 2008. 18: 1177-1189.
46. Pareja E, Gómez-Lechón MJ, Tolosa L. Induced pluripotent stem cells for the treatment of liver diseases: challenges and perspectives from a clinical viewpoint. Ann Transl Med. 2020. 8: 566-566.
47. Di-Iacovo N, Pieroni S, Piobbico D, Castelli M, Scopetti D, et al. Liver Regeneration and Immunity: A Tale to Tell. Int J Mol Sci. 2023. 24: 1176-1176.
48. Zheng W, Yang L, Jiang S, Chen M, Li J, Liu Z, et al. Role of Kupffer cells in tolerance induction after liver transplantation. Front Cell Dev Biol. 2023;11(1179077).
49. Zanna MY, Yasmin AR, Omar AR, Arshad SS, Mariatulqabtiah AR, Nur-Fazila SH, et al. Review of Dendritic Cells, Their Role in Clinical Immunology, and Distribution in Various Animal Species. Int J Mol Sci. 2021;22(15):8044.
50. Fucikova J, Palova-Jelinkova L, Bartunkova J, Spisek R. Induction of Tolerance and Immunity by Dendritic Cells: Mechanisms and Clinical Applications. Front Immunol. 2019. 10: 2393.
51. Zhuang Q, Cai H, Cao Q, Li Z, Liu S, Ming Y. Tolerogenic Dendritic Cells: The Pearl of Immunotherapy in Organ Transplantation. Front Immunol. 2020. 11: 552988.
52. Yoo S, Ha SJ. Generation of Tolerogenic Dendritic Cells and Their Therapeutic Applications. Immune Netw. 2016. 16: 52.
53. Beriou G, Moreau A, Cuturi MC. Tolerogenic dendritic cells. Curr Opin Organ Transplant. 2012. 17: 42-47.
54. Nyesiga GD, Pool L, Englezou PC, Hylander T, Ohlsson L, Appelgren D, et al. Tolerogenic dendritic cells generated in vitro using a novel protocol mimicking mucosal tolerance mechanisms represent a potential therapeutic cell platform for induction of immune tolerance. Front Immunol. 2023. 14: 1045183.
55. Reis C, Gouveia B, Rijo P, Gonçalo T. Good manufacturing practices for medicinal products for human use. J Pharm Bioallied Sci. 2015. 7: 87.
56. María José Mansilla, Catharien M U Hilkens, Eva María Martínez-Cáceres. Challenges in tolerogenic dendritic cell therapy for autoimmune diseases: the route of administration. PubMed Cent. 2023. 3: 1.
57. Tasdogan BE, Ma M, Simsek C, Saberi B, Gurakar A. Update on Immunosuppression in Liver Transplantation. Euroasian J Hepato-Gastroenterol. 2019. 9: 96-101.
58. Kapałczyńska M, Kolenda T, Przybyła W, Zajączkowska M, et al. 2D and 3D Cell Cultures – a Comparison of Different Types of Cancer Cell Cultures. Arch Med Sci. 2016. 14: 4.
59. Zhao Z. Organoids. Nat Rev Methods Primer. 2022. 2: 1-21.
60. Harrison SP, Siller R, Tanaka Y, Chollet ME, de la Morena-Barrio ME, Xiang Y, et al. Scalable production of tissue-like vascularized liver organoids from human PSCs. Exp Mol Med. 2023. 55: 2005-24.
61. Hyo Jin Kim, Kim G, Yoo K, Hye Min Kim, Yu Jin Jang, Jo S, et al. Generation of multilineage liver organoids with luminal vasculature and bile ducts from human pluripotent stem cells via modulation of Notch signaling. Stem Cell Res Ther. 2023;14: 1.
62. Ochando J, Ordikhani F, Jordan S, Boros P, Thomson AW. Tolerogenic dendritic cells in organ transplantation. Transpl Int. 2019. 33:113-27.
63. Jonny, Sitepu EC, Nidom CA, Wirjopranoto S, Sudiana IK, Ansori ANM, et al. Ex Vivo-Generated Tolerogenic Dendritic Cells: Hope for a Definitive Therapy of Autoimmune Diseases. Curr Issues Mol Biol. 2024;46):4035–48.
64. Harris DT. Biobanking and Regenerative Medicine: An Overview. J Clin Med. 2018.7: 131.