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From organ replacement to functional restoration: A paradigm shift in liver failure therapy

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SUMMARY: Liver transplantation has long been the definitive treatment for end-stage liver diseases, and yet its clinical use remains constrained by donor shortages, surgical risks, and the burden of lifelong immunosuppression. Emerging regenerative strategies, and particularly chemically induced liver progenitors (CLiPs), are reshaping this paradigm by enabling functional restoration rather than organ replacement. CLiP technology utilizes small-molecule-mediated partial reprogramming of mature hepatocytes into proliferative progenitor-like cells, which can be expanded and re-differentiated into functional hepatic lineages. This commentary discusses the conceptual shift from replacement to regeneration, it evaluates the clinical positioning of CLiP-based therapies, and it highlights key translational challenges. Rather than serving as a complete substitute for liver transplantation, such approaches may significantly reduce transplant demand by restoring critical hepatic function in selected patients.

Keywords: liver transplantation, chemically induced liver progenitors, regeneration

1. Introduction

Liver transplantation represents one of the most successful therapeutic interventions for end-stage liver diseases in modern medicine. Nevertheless, its clinical efficacy is inherently restricted by structural limitations, most notably the global shortage of donor organs and the risks associated with major surgery and lifelong immunosuppression. Despite advances in surgical techniques and perioperative care, a substantial proportion of patients with end-stage liver disease remain ineligible for transplantation or die while on waiting lists (*1,2*). These challenges have prompted a growing interest in alternative strategies that can restore liver function without requiring whole-organ replacement.

The liver possesses a remarkable intrinsic regenerative capacity, capable of recovering mass and function following injury (*3*). In chronic liver diseases such as cirrhosis or non-alcoholic steatohepatitis (NASH), however, this regenerative potential becomes impaired (*4*). Therapeutic approaches that can reactivate or augment endogenous repair mechanisms may therefore offer a viable alternative to transplantation. Among recent advances in regenerative medicine, chemically induced liver progenitors (CLiPs) have emerged as a promising candidate, suggesting that the future of end-stage liver disease treatment may lie not in replacing the organ, but in restoring its residual function. A historical overview of the evolving treatment strategies for liver failure is summarized in Table 1.

2. Current development of CLiP technology

The development of CLiPs stems from in-depth investigations into hepatocyte plasticity. This technology is based on the partial reprogramming of mature hepatocytes using defined small-molecule cocktails, converting them into proliferative progenitor-like cells with bipotent differentiation capacity (Figure 1) (*5,6*). Unlike induced pluripotent stem cells (iPSCs), which require complete dedifferentiation into a pluripotent state (*7*), CLiPs retain lineage restriction, thereby reducing the risk of tumorigenicity and improving differentiation fidelity (*8*). This lineage-constrained plasticity represents a key conceptual advance in regenerative biology. Although small-molecule cocktails inherently carry the potential risk of inducing genomic instability during cellular reprogramming (*9*), recent studies have yielded experimental data supporting the long-term safety of chemically induced hepatic cells. In a murine model, transplantation of chemically induced hepatocyte-like cells (ciHeps) exhibited no tumorigenic potential in either *in vitro* or *in vivo* settings, substantiated by comprehensive safety evaluations throughout the

Table 1. Historical stages and core characteristics of liver failure treatment paradigms

Stage	Timeframe	Representative Technologies/Strategies
Stage I: Symptomatic support and conservative management	1950s-1970s	Hepatoprotective drugs, nutritional support, ascites drainage
Stage II: Organ replacement and liver transplantation era	1980s-present	Orthotopic liver transplantation, living donor liver transplantation, split liver transplantation
Stage III: Cell therapy and regenerative medicine exploration	2000s-2010s	Hepatocyte transplantation, bone marrow stem cells, mesenchymal stem cells
Stage IV: Functional restoration and chemically induced reprogramming	2017-present	Chemically induced liver progenitors (CLiPs), chemically induced hepatic-like cells (ciHeps), hepatocyte-derived liver progenitor-like cells (HepLPCs)

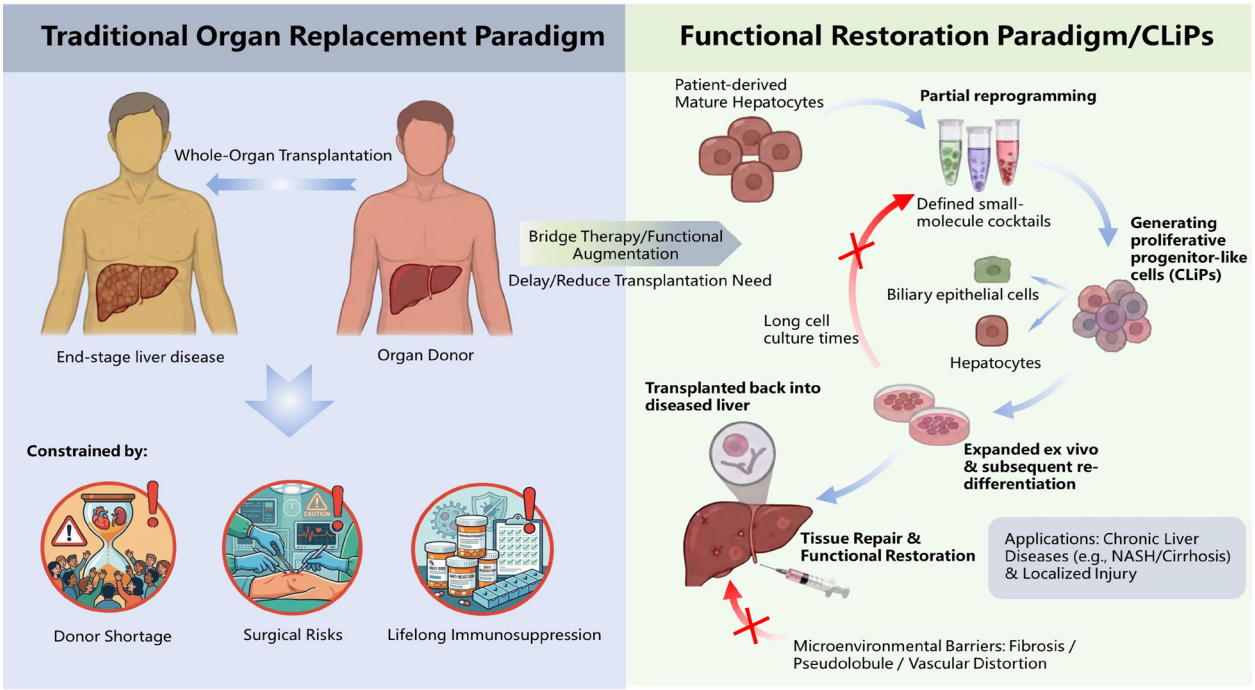

Figure 1. Schematic illustration of the paradigm shift from conventional liver transplantation to CLiP-based functional liver regeneration. *Abbreviations*: CLiPs, chemically induced liver progenitors; NASH, non-alcoholic steatohepatitis; ex vivo, outside the organism.

experimental period (*10*). Moreover, human chemically derived hepatic progenitors (hCdHs) retained a normal karyotype following at least 10 passages of self-renewal, thereby confirming their genomic stability (*11*). Although direct long-term (>1 year) tumorigenicity data specifically for CLiPs remain limited (*12*), these findings from chemically induced hepatic lineage cells offer persuasive empirical evidence regarding the safety advantages of lineage-constrained reprogramming over pluripotent approaches. However, recent evidence from a rat model of CLiP transplantation suggests that CLiPs may be susceptible to innate immune attack *in vivo*, raising additional safety considerations regarding immunogenicity (*13*).

In clinical practice, the critical threshold for meaningful hepatic recovery is highly dependent on the baseline quality of the liver parenchyma. While classic partial hepatectomy models establish that a healthy liver remnant of 20-25% is sufficient to sustain metabolic homeostasis and survival, this volumetric safety margin increases significantly in the presence of chronic liver disease (*14*). For patients with cirrhosis, surgical and radiological consensuses mandate a minimum retained liver volume of 40-50% to prevent post-procedural hepatic failure (*15*). This elevated requirement reflects a profound disconnect between macroscopic liver volume and actual functional capacity, driven by extensive fibrosis, pseudolobule formation, and microvascular distortion. Consequently, the therapeutic advantage of CLiPs lies in their capacity to deliver high-quality, functional hepatic mass. By directly replenishing the functional cellular pool rather than relying on the regeneration of compromised tissue, CLiP-based therapies have the potential to bypass the prohibitive

volumetric thresholds inherent to end-stage liver disease, achieving clinical stabilization without the need for massive structural regeneration.

Preclinical studies have demonstrated that CLiP-derived cells can engraft into injured liver tissue and contribute to functional recovery. In animal models, these cells have shown the capacity to repopulate damaged liver parenchyma and improve survival outcomes, with their functions mainly reflected in the following three aspects. First, CLiPs possess potent regenerative and repopulation capacity. A study by Katsuda *et al*. (*16*) demonstrated that rat CLiPs achieved a liver repopulation efficiency of 75-90% in cDNA-uPA/SCID mice, which was significantly higher than that of conventional hepatocyte transplantation. Second, CLiPs exhibit bipotent differentiation potential. *In vitro* 3D culture studies have confirmed that rat CLiPs can spontaneously form cystic structures containing both hepatocyte lineage and cholangiocyte lineage cells, suggesting a cellular basis for reconstructing complex hepatic tissue architecture (*17*). Third, CLiPs also possess important paracrine functions. Fukumoto *et al*. (*18*) successfully induced CLiPs from steatotic livers using a miniature pig model and further demonstrated that although the number of extracellular vesicles (EVs) derived from CLiPs in the disease group was lower than that in the normal group, their *in vivo* proliferative capacity was higher. In addition, these secreted factors may play an important role in the anti-fibrotic effects of CLiPs (*19*). Moreover, CLiPs can be generated from autologous hepatocytes, potentially eliminating the need for immunosuppressive therapy and overcoming one of the major limitations of liver transplantation (*20*). These findings support the feasibility of CLiP-based approaches as a form of cell-based liver regeneration.

Rather than positioning CLiPs as a direct replacement for liver transplantation, a more appropriate stance may be to consider this technology within a complementary therapeutic framework. This is particularly relevant for end-stage liver disease accompanied by severe structural disruption, including hepatic fibrosis, pseudolobule formation, and distortion of the vascular architecture (*21*). Despite demonstrated benefits in hepatic functional recovery and fibrosis resolution, the capacity of CLiPs to achieve definitive structural reconstruction remains unproven; specifically, direct evidence demonstrating the restoration of normal vascular architecture and the reversal of pseudolobules has yet to be established. Therefore, for liver diseases characterized by severe structural disorganization, such as portal hypertension, CLiP-based therapeutic strategies are best regarded as a form of functional augmentation, helping patients maintain essential liver function while serving as a bridge between medical management and organ transplantation.

For different types of liver disease, the use of CLiPs should focus on different therapeutic priorities (*22*). Several potential clinical applications for CLiP technology can be envisioned. First, the regenerative and differentiation capacity of CLiP therapy may function as a bridge to transplantation, maintaining hepatic function in patients with end-stage liver disease who are awaiting donor organs. It may also provide a therapeutic option for those who are not candidates for transplantation due to age or comorbidities. Second, CLiPs may be particularly relevant in earlier stages of chronic liver disease, including NASH and fibrosis, where disease progression may still be modifiable (*23*). In such cases, CLiPs have anti-fibrotic effects and improve liver function through their paracrine activity, which could delay or even obviate the need for transplantation. Occurring in approximately 10% of patients, post-hepatectomy liver dysfunction (LD) is a serious complication following liver resection and is associated with increased postoperative mortality and morbidity (*24*). Currently, no effective treatments are available to support postoperative liver regeneration. The dual action of CLiPs, which combines rapid paracrine support with direct cell engraftment, may offer a novel therapeutic approach for this condition. Unlike in chronic fibrosis, the remnant liver tissue in LD retains a relatively intact structure, providing favorable conditions for CLiP homing and integration. Moreover, a study by Viswanathan *et al*. (*25*) demonstrated that in an APAP-induced acute liver failure model, hepatocyte transplantation rescued mice without the need for hepatic repopulation, relying solely on paracrine factors. This finding suggests that in acute settings, CLiPs may similarly have rapid anti-apoptotic and anti-inflammatory effects through paracrine pathways, even before cell integration occurs.

3. Challenges in CLiP technology

Despite its promise, significant translational challenges remain. A 2025 review in *Nature Reviews Clinical Oncology* noted that autologous products require individualized manufacturing processes that are time-consuming and costly, with each product usable in only one patient (*26*). Similarly, a 2024 article in *The Journal of Immunology* pointed to challenges in patient applicability, safety, and efficacy consistency (*27*). These limitations of autologous cell therapies are equally pertinent to CLiPs.

One of the primary obstacles is scalability. Autologous cell therapies require individualized manufacturing processes, which are complex, time-consuming, and costly (*28*). Standardizing production while ensuring safety, potency, and reproducibility will be critical for clinical adoption. In addition, the long-term safety of partially reprogrammed cells must be carefully evaluated, particularly with regard to genomic stability and oncogenic risk (*29*).

Another critical challenge is the temporal disparity in therapeutic application. For chronic liver diseases, the hepatic microenvironment is relatively stable with

progressive yet slow injury, making autologous CLiPs derived from the patient's own hepatocytes a feasible approach. For acute liver injury or post-hepatectomy liver dysfunction, however, the processes of autologous cell procurement, reprogramming, and *in vitro* expansion are time-consuming (*30*), rendering the manufacturing timeline severely mismatched with the narrow therapeutic window. In such urgent settings, allogeneic CLiPs banks or "off-the-shelf" universal products are urgently needed, although these would raise additional issues regarding immune compatibility and long-term safety.

Economic considerations also represent a major barrier. The high cost of personalized cell therapies raises important questions regarding reimbursement and healthcare system integration. Without innovative funding models, the accessibility of such treatments may remain limited. Moreover, rigorous clinical trials need to be conducted to establish comparative effectiveness relative to existing therapies, including transplantation and pharmacological interventions (*31*).

In addition, regulatory and standardization challenges further complicate the clinical translation of CLiP-based therapies. The classification of CLiPs as advanced therapy medicinal products (ATMPs) imposes stringent regulatory requirements that vary considerably across jurisdictions. Establishing unified guidelines for good manufacturing practice (GMP) compliance, batch release criteria, and quality control metrics remains an urgent but unresolved issue (*32*).

At a broader level, the development of CLiPs reflects a fundamental shift in the conceptual framework of organ failure treatment. Traditional approaches have focused on replacing damaged organs, whereas emerging strategies aim to restore function by leveraging the plasticity of differentiated cells. This shift from organ replacement to functional restoration may have far-reaching implications not only for liver disease but for regenerative medicine as a whole.

In summary, CLiP technology presents a landscape of both promise and challenge. Its primary strengths, including a lower oncogenic profile relative to iPSCs, robust bipotent differentiation, and the potential for autologous application, position it as a frontrunner in regenerative hepatology. However, significant caveats remain: its capacity for structural reconstruction within severely distorted cirrhotic microenvironments is still unverified, framing its current role more as a functional augmentation than a definitive structural cure. Moreover, the logistical hurdles of autologous manufacturing—characterized by prolonged timelines and high costs—restrict its utility in acute settings where the therapeutic window is minimal. Coupled with emerging concerns regarding immunogenicity and the scarcity of long-term safety data, CLiPs are best integrated into a complementary therapeutic framework alongside liver transplantation. Future clinical success will hinge upon precise patient stratification, stage-specific application, and the successful maturation of universal, off-the-shelf products.

4. Conclusion

CLiPs exemplify a new generation of regenerative therapies that prioritize functional restoration over organ replacement. While liver transplantation will remain indispensable for patients with irreversible organ failure, CLiP-based approaches may significantly reduce transplant demand by enabling partial recovery of hepatic function. As clinical translation progresses, the success of this paradigm will depend on its ability to deliver safe, effective, and scalable therapies. Ultimately, the future of liver disease treatment may lie not in replacing the liver, but in repairing it.

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