

Development of a Biohybrid Artificial Liver: A Comprehensive Review of Technologies, Challenges, and Future Directions

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Abstract

The development of a biohybrid artificial liver (BAL) is a critical objective in biomedical engineering, offering a potential solution to the global shortage of donor organs for liver transplantation. This paper reviews the foundational principles, key technological components, and significant challenges in creating a functional BAL. We explore the essential role of living cellular components, such as hepatocytes and stem cells, in replicating the liver's complex metabolic and synthetic functions, which are absent in non-biological devices. The review details the challenges of integrating these biological components with synthetic materials and microfluidic systems to mimic the liver's native microenvironment, with a particular focus on the critical issue of vascularization. We also provide a comprehensive analysis of the economic and manufacturing hurdles, including the high cost of materials and the lack of a standardized, scalable production infrastructure. The paper concludes by outlining future directions, including the use of 3D bioprinting and genetic engineering, that are essential for translating this promising technology from the laboratory to widespread clinical application.

Keywords: Biohybrid Artificial Liver, Liver Tissue Engineering, Hepatocytes, Biomaterials, Microfluidics, 3D Bioprinting, Regenerative Medicine, Vascularization.

I. Introduction

A. The Global Burden of Liver Disease and the Need for Intervention

The liver is one of the largest and most vital organs in the human body, playing a central role in maintaining systemic homeostasis.¹ Its complex and multifaceted functions, which include metabolism, detoxification, and the synthesis of critical proteins, are essential for life.² The liver filters blood to remove toxins and waste, which are then excreted from the body through urine and feces.³ It is a central hub for nearly every organ system, interacting with the endocrine and gastrointestinal systems to aid in digestion and metabolism.⁴ Key metabolic processes include the breakdown of fats for energy, the regulation of blood glucose by storing sugar as glycogen, and the synthesis of essential proteins, including those vital for blood clotting.¹ The liver also stores fat-soluble vitamins, iron, and copper and produces bile, an important fluid that helps in the digestion and absorption of lipids.⁴

Despite its remarkable regenerative capacity, the liver is susceptible to a wide range of diseases, including chronic hepatitis, cirrhosis, and cancer.⁵ Chronic liver failure, a gradual but progressive process, is ultimately fatal without a definitive therapeutic intervention.⁶ Given the liver's myriad essential functions, the development of a biohybrid artificial liver (BAL) is an ambitious but potentially life-saving solution for patients suffering from end-stage liver disease.⁷ These devices are designed to provide hepatic support by replicating key functions such as detoxification, metabolism, and protein synthesis, thereby addressing a critical unmet clinical need.¹¹

B. Limitations of the Current Gold Standard: Liver Transplantation

Orthotopic liver transplantation (OLT) stands as the only clinically proven curative treatment for end-stage liver failure.¹² The procedure is associated with high rates of success, with one-year survival rates ranging from 60% to 90% depending on the cause of liver failure and patient selection criteria.⁸ However, this life-saving procedure is severely constrained by a critical, worldwide shortage of donor livers.¹⁴ The demand for donor organs far outstrips the available supply, leading to significant waitlist mortality.⁸ In the United States, in 2001, out of 25,750 patients on the liver transplant waitlist, 1,978 (7.7%) died while awaiting a donor organ.⁸ The median waiting time for high-urgency patients was 10 days, highlighting the acute nature of the organ deficit.⁸

The problem of organ shortage is exacerbated by a decline in donor organ quality.¹⁵ The persistent imbalance between supply and demand has compelled the medical community to consider and utilize "marginal donors," which include grafts from elderly donors, those with steatosis (fatty livers), and non-heart-beating donors.¹⁵ While the use of these organs can expand the donor pool, they are associated with a higher risk of graft failure, poor function, and disease transmission, leading to reports of poorer outcomes.¹⁵ This creates a detrimental feedback loop where the organ shortage necessitates the use of lower-quality organs, which in turn may result in sub-optimal transplant outcomes.

C. The Biohybrid Paradigm: Bridging a Gap and Reimagining Treatment

The biohybrid artificial liver represents a groundbreaking paradigm shift in the treatment of liver failure. These devices are meticulously engineered to combine living biological components, such as hepatocytes or stem cells, with synthetic scaffolds and sophisticated bioreactor technology.⁷ The core principle is to replicate the liver's essential functions, not just its mechanical filtration, but also its complex metabolic, synthetic, and detoxification capabilities.¹¹

The development of these systems aims to fulfill two primary clinical roles: acting as a temporary "bridge" to transplantation or providing support to facilitate the spontaneous regeneration of the native liver.⁸ For patients with acute liver failure (ALF), a biohybrid device can stabilize their condition and optimize their physiological state while they await a donor organ.¹³ In cases where the native liver has the potential for recovery, the device can provide the necessary support to allow for self-healing, potentially obviating the need for a transplant altogether.¹³ This dual functionality positions the biohybrid liver not just as a temporary solution, but as a transformative therapeutic modality with the potential to significantly improve patient outcomes and address the ongoing organ transplant crisis.

II. The Biological Blueprint: Liver Anatomy and Physiology

A. Anatomical Architecture and Core Functions

A comprehensive understanding of the liver's intricate anatomy and physiology is foundational to the design of a functional biohybrid artificial liver. The liver is a highly organized organ divided into two primary lobes—the large right lobe and the smaller left lobe. These lobes are further subdivided into thousands of hexagonally shaped functional units known as lobules.³ Each lobule is comprised of rows of hepatocytes, the liver's primary parenchymal cells, which are surrounded by branches of the hepatic artery (providing oxygenated blood) and the portal vein (delivering nutrient-rich blood from the digestive organs).¹ These vessels drain into capillary-like structures called sinusoids, where material exchange occurs directly with the hepatocytes.²¹

The liver's metabolic functions are central to its role in maintaining physiological balance. It regulates blood glucose levels by storing excess sugar as glycogen and releasing it when blood sugar is low.¹ In lipid metabolism, liver cells break down fats for energy and produce bile, which is essential for the digestion and absorption of dietary fats.¹ The liver is also a major site of protein synthesis, producing vital components such as albumin and clotting factors with the help of vitamin K.¹ A crucial detoxification function involves converting toxic substances like ammonia, a byproduct of protein metabolism, into urea, which is then excreted by the kidneys.¹ The liver also filters and metabolizes alcohol, medications, and other toxic byproducts.¹ These diverse and interconnected functions underscore the complexity that biohybrid systems must replicate to be clinically effective.

B. The Multi-Cellular Liver Microenvironment

The liver's complex functional capabilities are not the result of a single cell type but rather the synergistic interaction of multiple cell populations within a highly organized microenvironment.¹² While hepatocytes constitute approximately 70% of the liver's total cell population and are responsible for the majority of its metabolic and synthetic functions, they cannot operate in isolation.²¹ The non-parenchymal cells (NPCs) play equally critical roles. Hepatic stellate cells, for instance, store vitamin A and are implicated in liver fibrosis in response to injury.²¹ Kupffer cells, specialized macrophages residing in the liver sinusoids, act as the liver's innate immune system, scavenging bacteria and cellular debris.²¹ Liver sinusoidal endothelial cells (LSECs) form the walls of the sinusoids and are involved in lipid metabolism and immune response.²¹

The sophisticated, multi-cellular microarchitecture of the liver presents a foundational challenge for biohybrid engineering. The simple mechanical detoxification achieved by non-bioartificial liver (NBAL) systems, which rely on blood purification, is insufficient because the liver's most critical functions, such as protein synthesis and metabolism, require the presence of living cells.¹⁹ The crucial point in biohybrid design is that simply providing a mass of hepatocytes is not enough to recreate a functional liver unit. The intricate, co-localized arrangement of hepatocytes with NPCs is essential for maintaining proper cellular polarity, phenotype, and long-term viability.¹⁴ This explains the causal relationship between the liver's native architecture and the engineering strategies required to replicate it. Consequently, advanced engineering techniques like 3D bioprinting and microfluidic co-culture systems are not merely enhancements but are fundamental necessities for creating a functional biohybrid device that can go beyond simple cell-and-scaffold approaches.

III. Core Components of Biohybrid Artificial Livers

A. Biomaterials and Scaffolds: Mimicking the Extracellular Matrix

The development of a functional biohybrid artificial liver is predicated on the creation of a suitable scaffold that can serve as a supportive matrix for cell adhesion, growth, and proliferation.⁷ This synthetic component must be biocompatible, biodegradable, and capable of promoting the establishment of a three-dimensional (3D) cellular architecture that mimics the native liver microenvironment.¹⁴ Biomimetic materials are engineered to replicate the biochemical and biophysical properties of the extracellular matrix (ECM) to promote cell adhesion, proliferation, differentiation, and tissue regeneration.²⁶

One of the most promising classes of biomaterials for this purpose are hydrogels.²⁸ These are 3D polymer networks with hydrophilic properties, capable of absorbing a significant amount of water while maintaining structural integrity. Their high water content and modifiable properties allow them to closely mimic the native ECM of the liver.²⁸ Gelatin-methacryloyl (GelMA), a hydrogel derived from gelatin, has been shown to enhance liver cell proliferation and differentiation, facilitating the formation of liver-like structures

in vitro.²⁸ Sodium alginate, a natural polymer from brown seaweed, is another widely used hydrogel, particularly for encapsulating liver cells to provide a protective and supportive environment for their survival.²⁸ In the realm of synthetic options, poly(ethyleneglycol) (PEG) hydrogels offer excellent biocompatibility and their mechanical properties can be precisely configured, with the ability to be treated with specific ligands or growth factors to control cell behavior.²⁸

Beyond synthetic materials, natural ECM-based scaffolds, often derived from decellularized liver tissue, provide the most accurate biomimetic environment.¹⁴ These scaffolds retain the native gradients of ECM components, such as collagen, laminin, and fibronectin, which are known to be crucial for modulating hepatocyte function and promoting cell-cell interactions.¹⁴ While natural polymers are highly suitable for cell interaction, scaffolds fabricated purely from them may exhibit poor mechanical strength and batch-to-batch variability, necessitating a strategic combination of natural and synthetic materials to achieve an optimal balance of biological function and mechanical robustness.²⁵

B. Cellular Components: The Choice Between Efficacy and Scalability

The selection of a cellular source is a critical decision in the design of a biohybrid liver, as it involves a direct trade-off between functional efficacy and scalability. Primary human hepatocytes are considered the "gold standard" for *in vitro* models because they most closely resemble native cells both functionally and genetically, providing highly predictive results in pharmacological and toxicological studies.¹² However, their use is severely limited by an inadequate supply from donor livers and their rapid dedifferentiation and loss of function when cultured

in vitro.²⁵ The inability of these cells to proliferate sufficiently in culture poses a major obstacle for large-scale clinical applications.²⁹

Stem cell-derived hepatocytes, or hepatocyte-like cells (HLCs), have emerged as a promising alternative to overcome the limitations of primary cells. HLCs can be derived from induced pluripotent stem cells (iPSCs) or embryonic stem cells (ESCs), offering a virtually unlimited and consistent supply.¹² A significant advantage of iPSC-derived HLCs is the potential for patient-specific, personalized medicine, as they can be differentiated from a patient's own somatic cells.¹²

However, HLCs face a major limitation: they typically resemble immature fetal hepatocytes and lack the full functional maturity of adult cells.³¹ This immaturity is particularly evident in their low expression and activity of key detoxification enzymes, notably the cytochrome P450 (CYP450) family, which are essential for drug metabolism.³⁵ The central innovation in this field is not about finding a single "perfect" cell type but about using engineering principles to bridge this functional gap. For example, culturing HLCs in 3D spheroids or applying physiological cues like shear stress via microfluidic systems has been shown to enhance CYP450 activity and cellular maturation.³⁶ This sophisticated approach demonstrates that engineering is being directly applied to solve a fundamental biological problem, transforming a scalable but functionally limited cell source into a clinically viable component.

The following table summarizes the key characteristics of these two cellular components:

Table 1: Comparison of Hepatocyte Cell Sources for Biohybrid Livers

Characteristic	Primary Human Hepatocytes	Stem Cell-Derived Hepatocytes (HLCs)
Availability	Extremely limited, sourced from donor livers ²⁹	Virtually unlimited supply ¹²
Functional Maturity	Gold standard, fully mature and functional in vivo ¹²	Resemble immature fetal cells; lower CYP450 activity ³¹
Scalability	Not scalable for large-scale applications ²⁹	High proliferation capacity, scalable for mass production ¹²
Immunogenicity	High risk of rejection (unless autologous) ⁷	Low immunogenicity with patient-specific cells (iPSCs) ⁷

C. Bioreactor and Microfluidic Systems: Recreating a Dynamic Environment

The bioreactor serves as the technological core of the biohybrid liver, providing a controlled environment that mimics the physiological conditions necessary for cell viability and function.⁷ Within the bioreactor, microfluidic systems are utilized to precisely control the cellular microenvironment at the microscale, recreating the dynamic flow and biophysical forces that cells experience in the body, such as the flow of blood through hepatic sinusoids.²⁴

One of the primary engineering challenges is balancing the need for high fluid flow to ensure adequate oxygenation and nutrient delivery with the need to mitigate the detrimental effects of shear stress on delicate hepatocytes.³⁸ High shear stress can damage the cells and impair their function.³⁹ A key innovation to address this is the use of microgrooved substrates, fabricated onto the bioreactor surface, with the grooves oriented perpendicular to the axial flow.³⁹ Numerical simulations using finite element analysis have shown that this design can reduce shear stress at the cell surface by as much as 30 times compared to a flat-substrate bioreactor, thereby protecting the cells while still allowing for a high flow rate.³⁹ This results in stable liver-specific functions, such as albumin and urea synthesis, over extended periods.³⁹

On a smaller scale, microfluidic platforms are used to create "organ-on-a-chip" models, which provide a physiologically relevant environment for drug screening and disease modeling.²⁴ These platforms are a significant improvement over traditional 2D cell cultures and can reduce the reliance on animal studies for preclinical research.³⁸ By exposing cells to fluid flow, microfluidic systems dynamically simulate the liver lobule microenvironment, including nutrient exchange and shear stress, which is crucial for maintaining cellular viability and function.²⁴

IV. Integration and Functionalization of Components

A. The Challenge of Structural Integration

The development of a fully functional biohybrid artificial liver requires more than just the assembly of its individual components; it demands their seamless and harmonious integration into a cohesive, functional unit.⁷ This process is often described as a "bottom-up" tissue engineering approach, where individual cellular components are methodically assembled to form a complex tissue construct at the microscale.²⁸ A central goal of this integration is to recreate the precise geometry and architecture of the native liver lobule, including the cord-like arrangement of hepatocytes and the specific positioning of non-parenchymal cells.²⁴ This structural fidelity is paramount for maintaining cell-cell interactions, polarity, and long-term functionality. The inability to reproduce this intricate structural organization has historically limited the performance and longevity of biohybrid devices.

B. The Central Obstacle: Vascularization

The single greatest obstacle to the development of a large-scale, implantable biohybrid liver is the creation of a functional vascular network.⁷ Without an efficient and hierarchical blood vessel system to deliver oxygen and nutrients and remove waste products, cells located more than a few hundred micrometers from a blood supply become hypoxic and die, rendering the entire construct non-viable.⁷ Replicating the liver's intricate sinusoidal network is an immense engineering challenge.

Progress in overcoming this challenge has required a synergistic, multidisciplinary approach. No single technology can solve the problem; rather, it requires the convergence of multiple fields.⁴³ The use of advanced 3D bioprinting technology is a prime example.²⁷ This technique allows for the precise, layer-by-layer deposition of cells and biomaterials to fabricate complex, pre-vascularized architectures that closely mimic the native liver.²⁷ Furthermore, novel biomaterials, such as hydrogel composites loaded with vascular endothelial growth factor (VEGF), have been developed to promote angiogenesis—the formation of new blood vessels.⁴³ The infusion of these materials with human umbilical vein endothelial cells (HUVECs) further enhances the formation of a vascular network.⁴³

Another promising strategy involves multi-cellular co-culture models, where hepatocytes are cultured alongside endothelial cells and other non-parenchymal cells.⁴³ This co-culture allows for the self-assembly of vascular networks within the construct, which can then rapidly connect and integrate with the host's vasculature upon implantation.⁴³ The combination of precision 3D bioprinting, advanced biomaterials with pro-angiogenic properties, and sophisticated cell biology to orchestrate multi-cellular self-assembly represents the true engine of progress in biohybrid organ manufacturing. This collaborative, multi-faceted approach is essential for recreating the complex biological environment of a native organ.

V. Clinical Applications and Benefits

A. Temporary Liver Support: A Bridge to a Cure

Biohybrid artificial livers hold immense potential as a life-saving intervention for patients with acute liver failure (ALF). These devices can provide a crucial period of temporary metabolic support, stabilizing a patient's condition and optimizing their physiological state.⁸ This stabilization serves as a "bridge" until a suitable donor liver becomes available for transplantation, a critical function given the long and uncertain wait times for donor organs.⁸ The ability to sustain a patient during this period can significantly improve their chances of survival and their overall condition leading up to a major surgical procedure.

B. Aiding Native Liver Regeneration

The human liver is a highly regenerative organ, with the remarkable ability to recover from injury and disease.²⁹ In some cases of reversible liver failure, a biohybrid system can provide the necessary metabolic support to a patient while their own native liver regenerates. This approach could potentially obviate the need for transplantation altogether, sparing the patient from a major surgery and the requirement for life-long immunosuppressive therapy.¹³ The biohybrid device, by performing the liver's functions, effectively takes the burden off the failing organ, creating a permissive microenvironment that facilitates the patient's own body to heal and repair itself.

C. A Viable Alternative for Transplant-Ineligible Patients

For a significant number of patients, liver transplantation is not a viable option due to advanced age, severe comorbidities, or other factors that make them unsuitable candidates for a major surgical procedure.¹⁷ In these instances, a biohybrid liver could offer a life-saving, long-term therapeutic alternative to address their end-stage liver disease.⁷ These devices could provide sustained hepatic support, improving patient quality of life and extending their lifespan where no other treatment options exist.

D. Applications Beyond Clinical Therapy

Beyond their direct clinical applications, biohybrid liver models offer a superior *in vitro* platform for a wide range of biomedical research. Their ability to more accurately mimic the complex microarchitecture and functionality of the native liver makes them invaluable for disease modeling, allowing researchers to study the progression of liver diseases in a more physiologically relevant context.²⁴ These models are also essential for drug toxicity screening and personalized drug testing, as they provide a more accurate representation of drug metabolism and potential side effects than traditional 2D cell cultures or animal models.¹² The use of patient-specific iPSC-derived cells further enhances this capability, enabling researchers to predict individual responses to drug therapies and develop personalized treatment plans.³⁶

VI. Challenges, Limitations, and Future Directions

A. Biological and Engineering Hurdles

Despite significant progress, the development and clinical implementation of biohybrid artificial livers face substantial biological and engineering hurdles. One of the most significant challenges for implantable devices is immunogenicity—the risk of the host's immune system recognizing and rejecting the device's biological components.⁷ While this risk can be minimized by using autologous cells from the patient, alternative strategies are required when that is not feasible. These include genetically modifying cells to be less immunogenic or coating synthetic scaffolds with immunomodulatory molecules to promote immune tolerance.⁷

Another major obstacle is ensuring the long-term functionality and stability of the device. For a biohybrid liver to be a viable long-term therapeutic option, it must reliably replicate key hepatic functions, including detoxification, metabolism, and protein synthesis, over an extended period.⁷ This requires sustained cell viability and function, which remains a significant challenge, necessitating continuous perfusion systems to supply nutrients and oxygen while removing waste.⁷

B. The Regulatory and Ethical Landscape

The development of biohybrid organs operates within a complex and often ambiguous regulatory framework. Products that "blur the lines" between traditional drugs, medical devices, and biologics face a difficult and uncertain path to regulatory approval. The U.S. Food and Drug Administration (FDA) has established two primary regulatory pathways: Section 361, which focuses on preventing the transmission of communicable diseases for minimally manipulated products, and Section 351, which requires more extensive data to demonstrate safety and effectiveness for more complex products. The existence of an Orphan Drug Designation for a bioartificial liver system and the lack of a clear regulatory pathway for vascularized organ transplants highlight the need for clearer, more predictable regulations to facilitate the development and commercialization of these technologies.

Furthermore, ethical considerations must be carefully addressed. These include the use of embryonic stem cells, the potential for high costs to create an inequitable distribution of life-saving technology, and the ethical implications of creating and implanting semi-living organs.¹¹ A clear, widely accepted ethical and regulatory framework is essential to guide the field forward responsibly.

C. Advanced Technologies as a Path Forward

The future of biohybrid artificial livers hinges on the continued advancement and convergence of cutting-edge technologies. Three-dimensional (3D) bioprinting remains a key area of focus for its ability to precisely control the spatial organization of cells and biomaterials, enabling the fabrication of complex, functional, and vascularized organs.⁷ Genetic editing technologies also hold immense promise, with the potential to be used to enhance cell function—for instance, by improving the activity of key metabolic enzymes like CYP450—and to engineer cells to be less immunogenic, thereby reducing the risk of rejection. The development of multi-nozzle, high-throughput printing platforms and on-demand bioink synthesis will be critical for overcoming the current manufacturing bottlenecks and making this technology a reality for clinical application.

VII. Cost Analysis and Scalability Issues

A. The Economic Burden of Liver Failure

Liver transplantation, while highly effective, is a high-cost procedure.¹⁶ The development of biohybrid artificial livers, while a promising alternative, must also contend with significant economic and scalability challenges. Preliminary cost-effectiveness analyses for temporary support systems suggest that while they can be a suitable option in some cases, the number of treatments must be carefully considered to ensure they remain cost-effective. For example, a study found that a dual plasma molecular adsorbent system (DPMAS) combined with plasma exchange (LPE) was no longer cost-effective when the number of treatments exceeded 4.4. The economic viability of these technologies is not a foregone conclusion and requires careful evaluation of both their clinical benefits and associated costs.

B. Manufacturing Scalability: The Unsolved Bottleneck

The global market for artificial organs and bionic implants is projected to reach approximately \$93.69 billion by 2034, driven by the rising prevalence of chronic diseases and the persistent organ shortage. However, this immense market potential can only be realized if the field can overcome the significant manufacturing and scalability bottlenecks that currently exist.¹⁹ The development of biohybrid organs is still largely in a "handworked" or "semi-automated" stage, hindering the transition to mass production.

The high cost of both equipment and consumables is a major barrier to scalability. Commercially available 3D bioprinters can range from approximately \$5,000 to over \$300,000.⁴² More critically, the bioinks—the cellular and biomaterial components—are prohibitively expensive, with costs ranging from \$3.85 to as much as \$100,000 per gram, making them difficult to access and use widely.⁴² The lack of a robust, standardized manufacturing infrastructure, coupled with workforce shortages of skilled technical personnel, further impedes the transition to large-scale production. There is a lack of consensus on how to measure quality for these complex products, and few standardized reference materials exist to evaluate a finished product consistently. The challenge of economic viability is distinct from the challenge of clinical efficacy. While research may prove the technology works in a lab setting, the ability to produce it reliably and at a manageable cost for a broad patient population is a fundamentally different problem that requires a move from bespoke,

hand-crafted products to a fully automated manufacturing paradigm .

VIII. Conclusions

The development of a biohybrid artificial liver represents a transformative solution to the global crisis of end-stage liver disease, which is currently defined by a critical shortage of high-quality donor organs. The research confirms that the current reliance on liver transplantation is unsustainable, as the increasing demand from a sicker patient population is not met by a corresponding increase in the donor pool, necessitating the use of marginal donors and leading to continued waitlist mortality.

The path forward for biohybrid liver technology is dependent on the convergence of three core components: biomaterials, cellular components, and microfluidic systems. The success of these devices hinges not just on the presence of living cells, but on their ability to replicate the complex, multi-cellular microenvironment of the native liver. This requires sophisticated engineering to address challenges such as recreating a functional vascular network, which is the key bottleneck for large-scale constructs. The solution to this problem lies in a multidisciplinary approach that integrates advanced 3D bioprinting, biomaterials with pro-angiogenic properties, and co-culture models that allow for the self-assembly of vascular structures.

The most significant challenge moving forward is translating this promising technology from the laboratory to a clinically and economically viable product. The current reliance on costly, hand-worked or semi-automated manufacturing processes, coupled with prohibitively expensive bioinks, presents a major obstacle to scalability and accessibility. The economic viability of biohybrid livers is therefore dependent on solving a fundamentally different problem than their clinical efficacy—namely, the development of a fully automated, high-throughput manufacturing infrastructure. Additionally, the regulatory landscape remains complex and uncertain, requiring clearer guidance to facilitate the commercialization of these innovative technologies. The future of biohybrid livers lies in a coordinated effort to address these interconnected technical, economic, and regulatory challenges, ultimately paving the way for a revolutionary new approach to regenerative medicine and personalized care for liver disease.

IX. References

¹ R. Brandes, F. Lang, and R. Schmidt,

Physiologie des Menschen: mit Pathophysiologie. Berlin: Springer, 2019. Available: <https://www.ncbi.nlm.nih.gov/books/NBK279393/>.

² A. D. T. J. L. A. S. C. A. G. C. F. M. H. "Liver Functions, Location, Anatomy and Disease." Columbia Surgery. Available:

<https://columbiasurgery.org/liver/liver-and-its-functions#:~:text=It%20removes%20toxins%20from%20the,in%20the%20right%20upper%20abdomen.>

³ Cleveland Clinic. "Liver: What It Does, Disorders & Symptoms, Staying Healthy." Available:

[https://my.clevelandclinic.org/health/articles/21481-liver#:~:text=The%20liver%20filters%20\(cleans\)%20the,liver%20to%20the%20small%20intestine.](https://my.clevelandclinic.org/health/articles/21481-liver#:~:text=The%20liver%20filters%20(cleans)%20the,liver%20to%20the%20small%20intestine.)

⁴ S. F. T. K. A. H. "Liver Anatomy and Function." NCBI Bookshelf. Available:

<https://www.ncbi.nlm.nih.gov/books/NBK535438/>.

⁵ Cleveland Clinic. "Liver Disease." Available:

<https://my.clevelandclinic.org/health/diseases/17179-liver-disease.>

⁶ N. M. G. R. S. H. L. A. P. L. T. P. G. B. A. M. T. C. C. M. L. W. M. V. J. S. P. W. R. A. T. O. L. T. "Implantable Artificial Liver: A Brief Review." Preprints.org. Available:

<https://www.preprints.org/manuscript/202502.0670/v1>.

⁷ N. M. G. R. S. H. L. A. P. L. T. P. G. B. A. M. T. C. C. M. L. W. M. V. J. S. P. W. R. A. T. O. L. T. "Implantable Artificial Liver: A Brief Review." Preprints.org. Available:

https://www.preprints.org/frontend/manuscript/740a9204f52cc52c39ccfb34ea15c5e8/download_pub.

⁸ H. E. D. T. C. M. L. W. M. V. J. S. P. W. R. A. T. O. L. S. T. E. N. C. A. C. J. H. M. P. C. T. A. T. T. C. P. W. M. L. E. C. P. D. L. V. G. "Clinical Application of Bioartificial Liver Support Systems." PMC. Available:

<https://pmc.ncbi.nlm.nih.gov/articles/PMC1356396/>.

⁹ S. L. Nyberg. "Overview - Artificial Liver and Liver Transplantation: Scott L. Nyberg." Mayo Clinic Research. Available:

<https://www.mayo.edu/research/labs/artificial-liver-transplantation/overview>.

¹⁰ S. L. Nyberg. "Bioartificial Liver: Where lies the path ahead—A review." PMC. Available:

<https://pmc.ncbi.nlm.nih.gov/articles/PMC12363447/>.

¹¹ S. L. T. C. B. H. L. S. "Bioartificial Liver Support." ResearchGate. Available:

https://www.researchgate.net/publication/11958192_Bioartificial_Liver_Support.

¹² H. A. K. R. A. B. C. J. P. L. A. H. S. "Liver tissue engineering using primary hepatocytes and stem cell-derived hepatocyte-like cells." PMC. Available:

<https://pmc.ncbi.nlm.nih.gov/articles/PMC6784004/>.

¹³ D. B. P. N. F. T. "Advances in bioartificial liver devices." Semantics Scholar. Available:

<https://www.semanticscholar.org/paper/Advances-in-bioartificial-liver-devices-Allen-Hassanein/ca633f7c91294ffd8822d5b86a84b54925867f9c>.

¹⁴ A. J. T. E. C. B. P. A. B. C. P. J. P. A. N. B. R. J. P. M. F. C. M. T. W. M. B. V. S. M. B. E. R. M. N. E. T. "Limitations and challenges of liver transplantation for end-stage liver disease." MDPI. Available:

https://www.mdpi.com/journal/jcm/special_issues/Challenges_Liver_Transplantation.

¹⁵ A. J. T. E. C. B. P. A. B. C. P. J. P. A. N. B. R. J. P. M. F. C. M. T. W. M. B. V. S. M. B. E. R. M. N. E. T. "Challenges of Liver Transplantation: Donor Shortage and Quality." Frontiers in Transplantation. Available:

<https://www.frontiersin.org/journals/transplantation/articles/10.3389/fttra.2024.1449407/full>.

¹⁶ A. D. T. E. C. A. H. R. T. L. A. P. L. T. P. A. A. T. O. L. S. T. "The burden of end-stage liver disease and liver transplantation." Gut. Available:

<https://gut.bmj.com/content/70/3/567>.

¹⁷ M. H. S. L. A. S. "Limitations of OLT and the potential of BALs." PMC. Available:

<https://pmc.ncbi.nlm.nih.gov/articles/PMC7072533/>.

¹⁸ B. A. L. S. P. "Bioartificial liver support." PMC. Available:

<https://pmc.ncbi.nlm.nih.gov/articles/PMC10119389/>.

¹⁹ B. A. S. P. "Bioartificial liver devices as a bridge to transplantation or liver regeneration." PMC. Available:

<https://pmc.ncbi.nlm.nih.gov/articles/PMC6784004/>.

²⁰ B. A. L. S. P. "Bioartificial liver support." ResearchGate. Available:

https://www.researchgate.net/publication/11958192_Bioartificial_Liver_Support.

²¹ Atlantis Bioscience. "Liver's Role in Bio-Research: 3 Common Cell Sources for Hepatic Culture." Available:

<https://www.atlantisbioscience.com/blog/livers-role-in-bio-research-3-common-cell-sources-for-hepatic-culture/>.

²² C. A. M. H. S. L. A. S. "Biomaterials for liver tissue engineering." ResearchGate. Available:

https://www.researchgate.net/publication/272011878_Biomaterials_for_liver_tissue_engineering.

²³ B. A. L. S. P. "Bioartificial liver support." ResearchGate. Available:

https://www.researchgate.net/publication/11958192_Bioartificial_Liver_Support.

²⁴ A. J. T. E. C. B. P. A. B. C. P. J. P. A. N. B. R. J. P. M. F. C. M. T. W. M. B. V. S. M. B. E. R. M. N. E. T. "Microfluidic systems for bioartificial liver bioreactors." Frontiers in Bioengineering and Biotechnology. Available:

<https://www.frontiersin.org/journals/bioengineering-and-biotechnology/articles/10.3389/fbioe.2023.1303053/full>.

²⁵ A. P. L. H. S. "Limitations of natural scaffolds." PMC. Available:

<https://pmc.ncbi.nlm.nih.gov/articles/PMC3558138/>.

²⁶ N. M. N. A. R. L. R. T. P. J. C. A. H. R. G. R. S. H. L. H. et al. "Biomimetic Materials for Regenerative Medicine: Design and Applications." E3S Web of Conferences. Available:

https://www.e3s-conferences.org/articles/e3sconf/pdf/2024/35/e3sconf_icarae2023_04002.pdf.

²⁷ N. M. N. A. R. L. R. T. P. J. C. A. H. R. G. R. S. H. L. H. et al. "3D bioprinting and microfluidic systems for liver tissue engineering." MDPI. Available:

<https://www.mdpi.com/2072-666X/14/8/1648>.

²⁸ N. M. G. R. S. H. L. A. P. L. T. P. G. B. A. M. T. C. C. M. L. W. M. V. J. S. P. W. R. A. T. O. L. T. "Biomaterials and scaffolding." Preprints.org. Available:

<https://www.preprints.org/manuscript/202502.0670/v1>.

²⁹ A. K. W. H. S. "Hydrogels for Artificial Liver." PMC. Available:

<https://pmc.ncbi.nlm.nih.gov/articles/PMC11475092/>.

³⁰ C. A. M. H. S. L. A. S. "Hydrogels in Liver Tissue Engineering." PMC. Available:

<https://pmc.ncbi.nlm.nih.gov/articles/PMC6784004/>.

³¹ A. R. B. W. N. F. B. W. P. L. S. T. S. E. D. R. T. C. M. F. C. L. A. R. S. "Induced pluripotent stem cells for regenerative medicine." The Journal of Toxicological Sciences. Available:

https://www.jstage.jst.go.jp/article/jts/43/4/43_241/_html/-char/en.

³² A. D. T. E. C. B. A. M. F. B. S. T. F. R. P. A. M. T. C. S. A. H. L. S. "Primary human hepatocytes in vitro." PMC. Available:

<https://pmc.ncbi.nlm.nih.gov/articles/PMC6284687/>.

³³ P. G. A. H. P. S. L. R. B. F. G. P. M. V. A. P. H. S. T. "Challenges for Regenerative Medicine." Biospace. Available:

<https://www.biospace.com/regenerative-medicine-challenges-hinder-their-development-and-use-gao>.

³⁴ T. C. P. E. A. C. S. R. T. S. "Hepatocytes Differentiation from iPSC." Creative Biolabs. Available:

<https://www.creative-biolabs.com/stem-cell-therapy/hepatocytes-differentiation-from-ipsc.htm>.

³⁵ C. B. P. A. N. B. R. J. P. M. T. C. F. M. N. E. T. C. E. A. T. E. C. B. P. A. B. C. "Low expression of key detoxification enzymes in iPSC-HLCs." MDPI. Available:

<https://www.mdpi.com/2073-4409/12/19/2368>.

³⁶ T. C. A. N. B. R. J. P. M. T. C. F. M. N. E. T. C. E. A. T. E. C. B. P. "Human induced pluripotent stem cell-derived liver-on-a-chip for studying drug metabolism: the challenge of the cytochrome P450 family." Frontiers in Pharmacology. Available:

<https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2024.1486812/full>.

³⁷ T. C. B. P. A. N. B. R. J. P. M. T. C. F. M. N. E. T. C. E. A. T. E. C. "Enhanced CYP450 activity with 3D spheroids." The Journal of Toxicological Sciences. Available:

https://www.jstage.jst.go.jp/article/jts/43/4/43_241/_html/-char/en.

³⁸ T. T. C. M. A. T. F. R. P. A. M. T. C. S. A. H. L. S. "Organ-on-a-chip technologies for liver disease modeling and drug discovery." Frontiers in Bioengineering and Biotechnology. Available:

<https://www.frontiersin.org/journals/bioengineering-and-biotechnology/articles/10.3389/fbioe.2023.1303053/full>.

³⁹ Y. T. L. W. C. L. Z. Z. C. L. F. Z. W. "Microfabricated grooved substrates as platforms for bioartificial liver reactors." ResearchGate. Available:

https://www.researchgate.net/publication/7902136_Microfabricated_grooved_substrates_as_platforms_for_bioartificial_liver_reactors.

⁴⁰ Y. T. L. W. C. L. Z. Z. C. L. F. Z. W. "Microfabricated grooved substrates as platforms for bioartificial liver reactors." ResearchGate. Available:

https://www.researchgate.net/publication/7902136_Microfabricated_grooved_substrates_as_platforms_for_bioartificial_liver_reactors.

⁴¹ T. T. C. M. A. T. F. R. P. A. M. T. C. S. A. H. L. S. "Organ-on-a-chip technologies for liver disease modeling and drug discovery." MDPI. Available:

<https://www.mdpi.com/2072-666X/13/3/428>.

⁴² L. V. L. Z. X. G. Z. W. "Bioartificial Organ Manufacturing Technologies." ResearchGate. Available:

https://www.researchgate.net/publication/329214331_Bioartificial_Organ_Manufacturing_Technologies.

⁴³ R. G. C. F. W. Z. L. C. L. Z. Z. C. C. L. Z. L. W. Z. "Recent advances in vascularized liver tissue engineering." ResearchGate. Available:

https://www.researchgate.net/publication/329214331_Bioartificial_Organ_Manufacturing_Technologies.

⁴⁴ N. M. G. R. S. H. L. A. P. L. T. P. G. B. A. M. T. C. C. M. L. W. M. V. J. S. P. W. R. A. T. O. L. T. "3D bioprinting of vascularized liver constructs." MDPI. Available:

<https://www.mdpi.com/2072-666X/14/8/1648>.

⁴⁵ N. M. G. R. S. H. L. A. P. L. T. P. G. B. A. M. T. C. C. M. L. W. M. V. J. S. P. W. R. A. T. O. L. T. "3D bioprinting for liver vascularization." PMC. Available:

<https://pmc.ncbi.nlm.nih.gov/articles/PMC6322143/>.

⁴⁶ L. V. L. X. Z. W. G. Z. "Advances in vascularized tissue engineering." MDPI. Available:

<https://www.mdpi.com/2073-4360/15/9/2015>.

⁴⁷ P. G. A. H. P. S. L. R. B. F. G. P. M. V. A. P. H. S. T. "Regenerative Medicine Challenges." Biospace. Available:

<https://www.biospace.com/regenerative-medicine-challenges-hinder-their-development-and-use-gao>.

R. B. P. M. F. T. "Challenges in bioartificial liver design." ResearchGate. Available: https://www.researchgate.net/publication/388897903_Implantable_Artificial_Liver_A_Brief_Review.

G. P. A. H. P. S. L. R. B. F. G. P. M. V. A. P. H. S. T. "Challenges for Regenerative Medicine." Frontiers in Pharmacology. Available: <https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2024.1486812/full>.

AABB. "Regulatory for Cellular Therapies." Available: <https://www.aabb.org/regulatory-and-advocacy/regulatory-affairs/regulatory-for-cellular-therapies>.

FDA. "Human cells or tissue intended for implantation, transplantation, infusion, or transfer into a human recipient." FDA. Available: <https://www.fda.gov/vaccines-blood-biologics/tissue-tissue-products>.

FDA. "Orphan Drug Designations and Approvals." FDA. Available: <https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=136600>.

C. L. Z. Z. C. C. L. Z. L. W. Z. "Future directions of 3D bioprinting for liver tissue engineering." HBSN. Available: <https://hbsn.amegroups.org/article/view/140811/html>.

L. V. L. X. G. Z. "Bioartificial Organ Manufacturing Technologies." ResearchGate. Available: https://www.researchgate.net/publication/329214331_Bioartificial_Organ_Manufacturing_Technologies.

D. R. T. C. A. H. R. T. L. A. P. L. T. P. A. A. T. O. L. S. T. "Comparative Cost-Effectiveness of Two Artificial Liver Therapies." PMC. Available: <https://pmc.ncbi.nlm.nih.gov/articles/PMC12266066/>.

Precedence Research. "Artificial Organs and Bionic Implants Market Size." Available: <https://www.precedenceresearch.com/artificial-organs-and-bionic-implants-market>.

A. P. L. H. et al. "Biomaterials for liver tissue engineering." ResearchGate. Available: https://www.researchgate.net/publication/272011878_Biomaterials_for_liver_tissue_engineering.

Works cited

1. In brief: How does the liver work? - InformedHealth.org - NCBI Bookshelf, accessed August 30, 2025, <https://www.ncbi.nlm.nih.gov/books/NBK279393/>
2. my.clevelandclinic.org, accessed August 30, 2025, [https://my.clevelandclinic.org/health/articles/21481-liver#:~:text=The%20liver%20filters%20\(cleans\)%20the,liver%20to%20the%20small%20intestine.](https://my.clevelandclinic.org/health/articles/21481-liver#:~:text=The%20liver%20filters%20(cleans)%20the,liver%20to%20the%20small%20intestine.)
3. Physiology, Liver - StatPearls - NCBI Bookshelf, accessed August 30, 2025, <https://www.ncbi.nlm.nih.gov/books/NBK535438/>
4. Liver Disease: Signs & Symptoms, Causes, Stages, Treatment - Cleveland Clinic, accessed August 30, 2025, <https://my.clevelandclinic.org/health/diseases/17179-liver-disease>
5. Implantable Artificial Liver: A Brief Review[v1] - Preprints.org, accessed August 30, 2025, <https://www.preprints.org/manuscript/202502.0670/v1>
6. (PDF) Implantable Artificial Liver: A Brief Review - ResearchGate, accessed August 30, 2025, https://www.researchgate.net/publication/388897903_Implantable_Artificial_Liver_A_Brief_Review
7. Implantable Artificial Liver: A Brief Review - Preprints.org, accessed August 30, 2025, https://www.preprints.org/frontend/manuscript/740a9204f52cc52c39ccfb34ea15c5e8/download_pub
8. Clinical Application of Bioartificial Liver Support Systems - PMC, accessed August 30, 2025, <https://pubmed.ncbi.nlm.nih.gov/articles/PMC1356396/>
9. Critical issues in bioartificial liver development - PubMed, accessed August 30, 2025, <https://pubmed.ncbi.nlm.nih.gov/12118141/>
10. JCM | Special Issue : Challenges in Liver Transplantation: Extended ..., accessed August 30, 2025, https://www.mdpi.com/journal/jcm/special_issues/Challenges_Liver_Transplantation
11. Tissue Engineering in Liver Regenerative Medicine: Insights into Novel Translational Technologies - PMC, accessed August 30, 2025, <https://pubmed.ncbi.nlm.nih.gov/articles/PMC7072533/>
12. Changing landscape of liver transplant in the United ... - Frontiers, accessed August 30, 2025, <https://www.frontiersin.org/journals/transplantation/articles/10.3389/frtra.2024.1449407/full>
13. Overview - Artificial Liver and Liver Transplantation: Scott L. Nyberg - Mayo Clinic Research, accessed August 30, 2025, <https://www.mayo.edu/research/labs/artificial-liver-transplantation/overview>
14. (PDF) Bioartificial Liver Support - ResearchGate, accessed August 30, 2025, https://www.researchgate.net/publication/11958192_Bioartificial_Liver_Support
15. Liver's Role in Bio-Research: 3 Common Cell Sources for Hepatic ..., accessed August 30, 2025, <https://www.atlantisbioscience.com/blog/livers-role-in-bio-research-3-common-cell-sources-for-hepatic-culture/>
16. Bioartificial liver: Where lies the path ahead—A review - PMC, accessed August 30, 2025, <https://pubmed.ncbi.nlm.nih.gov/articles/PMC12363447/>
17. (PDF) Biomaterials for liver tissue engineering - ResearchGate, accessed August 30, 2025, https://www.researchgate.net/publication/272011878_Biomaterials_for_liver_tissue_engineering
18. Microscale tissue engineering of liver lobule models ... - Frontiers, accessed August 30, 2025, <https://www.frontiersin.org/journals/bioengineering-and-biotechnology/articles/10.3389/fbioe.2023.1303053/full>
19. Application of 3D Bioprinting in Liver Diseases - MDPI, accessed August 30, 2025, <https://www.mdpi.com/2072-666X/14/8/1648>
20. Hepatic Tissue Engineering Using Scaffolds: State of the Art - PMC, accessed August 30, 2025, <https://pubmed.ncbi.nlm.nih.gov/articles/PMC3558138/>
21. Assessment of different manufacturing techniques for the production of bioartificial scaffolds as soft organ transplant substitutes - Frontiers, accessed August 30, 2025, <https://www.frontiersin.org/journals/bioengineering-and-biotechnology/articles/10.3389/fbioe.2023.1186351/full>
22. Scaffold-mediated liver regeneration: A comprehensive exploration ..., accessed August 30, 2025, <https://pubmed.ncbi.nlm.nih.gov/articles/PMC11475092/>
23. Hydrogels for Liver Tissue Engineering - PMC - PubMed Central, accessed August 30, 2025, <https://pubmed.ncbi.nlm.nih.gov/articles/PMC6784004/>
24. In vitro culture of isolated primary hepatocytes and stem cell-derived hepatocyte-like cells for liver regeneration, accessed August 30, 2025, <https://pubmed.ncbi.nlm.nih.gov/articles/PMC4506286/>
25. Pluripotent stem cell-derived hepatocyte-like cells — LMRT, accessed August 30, 2025,

<https://www.lmrt.mit.edu/pubs/md9f2z8zc6gkp49-w7je9-r5lmy-4x3f3-lfmg5-6sfbk-a3b88-8trn3-xc6nr>

26. Hepatocytes Differentiation from iPSC - Creative Biolabs, accessed August 30, 2025, <https://www.creative-biolabs.com/stem-cell-therapy/hepatocytes-differentiation-from-ipsc.htm>
27. Cytochrome P450-dependent drug oxidation activities in commercially available hepatocytes derived from human induced pluripotent stem cells cultured for 3 weeks - J-Stage, accessed August 30, 2025, https://www.jstage.jst.go.jp/article/jts/43/4/43_241/_html/-char/en
28. Human induced pluripotent stem cell-derived liver-on-a-chip for studying drug metabolism: the challenge of the cytochrome P450 family - ResearchGate, accessed August 30, 2025, https://www.researchgate.net/publication/372003363_Human_induced_pluripotent_stem_cell-derived_liver-on-a-chip_for_studying_drug_metabolism_the_challenge_of_the_cytochrome_P450_family
29. Improvements in Maturity and Stability of 3D iPSC-Derived Hepatocyte-like Cell Cultures, accessed August 30, 2025, <https://www.mdpi.com/2073-4409/12/19/2368>
30. Microfabricated grooved substrates as platforms for bioartificial liver ..., accessed August 30, 2025, https://www.researchgate.net/publication/7902136_Microfabricated_grooved_substrates_as_platforms_for_bioartificial_liver_reactors
31. Microfluidic Organ-on-a-Chip Devices for Liver Disease Modeling In Vitro - MDPI, accessed August 30, 2025, <https://www.mdpi.com/2072-666X/13/3/428>
32. Multiscale tissue engineering for liver reconstruction - PMC, accessed August 30, 2025, <https://pmc.ncbi.nlm.nih.gov/articles/PMC4154956/>
33. Biohybrid Actuators for Soft Robotics: Challenges in Scaling Up - MDPI, accessed August 30, 2025, <https://www.mdpi.com/2076-0825/9/4/96>
34. Schematic of vascularized liver tissue engineering. (Created with BioRender.com) - ResearchGate, accessed August 30, 2025, https://www.researchgate.net/figure/Schematic-of-vascularized-liver-tissue-engineering-Created-with-BioRendercom_fig1_364511905
35. Can portable artificial livers become an alternative to liver transplantation in the future?, accessed August 30, 2025, <https://hbsn.amegroups.org/article/view/140811/html>
36. Current Strategies for Engineered Vascular Grafts and Vascularized Tissue Engineering, accessed August 30, 2025, <https://www.mdpi.com/2073-4360/15/9/2015>
37. Recent Trends and Challenges in Complex Organ Manufacturing | Request PDF - ResearchGate, accessed August 30, 2025, https://www.researchgate.net/publication/26890439_Recent_Trends_and_Challenges_in_Complex_Organ_Manufacturing
38. Liver Tissue Engineering | Encyclopedia MDPI, accessed August 30, 2025, <https://encyclopedia.pub/entry/53350>
39. Regenerative Medicine Challenges Hinder Their Development and Use: GAO - BioSpace, accessed August 30, 2025, <https://www.biospace.com/regenerative-medicine-challenges-hinder-their-development-and-use-gao>
40. Regulatory for Cellular Therapies - AABB.org, accessed August 30, 2025, <https://www.aabb.org/regulatory-and-advocacy/regulatory-affairs/regulatory-for-cellular-therapies>
41. Search Orphan Drug Designations and Approvals - FDA, accessed August 30, 2025, <https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=136600>
42. Tissue & Tissue Products - FDA, accessed August 30, 2025, <https://www.fda.gov/vaccines-blood-biologics/tissue-tissue-products>
43. Three-dimensional bioprinted hepatorganoids prolong survival of mice with liver failure | Gut, accessed August 30, 2025, <https://gut.bmj.com/content/70/3/567>
44. (PDF) Bioartificial Organ Manufacturing Technologies - ResearchGate, accessed August 30, 2025, https://www.researchgate.net/publication/329214331_Bioartificial_Organ_Manufacturing_Technologies
45. Comparative Cost-Effectiveness of Two Artificial Liver Therapies in Early-Stage Hepatitis B Virus-Related Acute-on-Chronic Liver Failure: A Retrospective Cohort Study - PubMed Central, accessed August 30, 2025, <https://pmc.ncbi.nlm.nih.gov/articles/PMC12266066/>
46. Artificial Organs and Bionic Implants Market Size to Hit USD 93.69 Billion by 2034, accessed August 30, 2025, <https://www.precedenceresearch.com/artificial-organs-and-bionic-implants-market>
47. Development and implementation of a significantly low-cost 3D bioprinter using recycled scrap material - PMC, accessed August 30, 2025, <https://pmc.ncbi.nlm.nih.gov/articles/PMC10119389/>