Advances in Bioartificial Liver Devices

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Liver failure is the cause of death for over 30,000 patients each year in the United States alone. When this process occurs in healthy individuals with normal livers, it is termed acute liver failure (ALF). Loss of liver function that complicates chronic liver disease is termed acute-on-chronic liver failure. Liver transplantation is curative for ALF and acute-on-chronic liver failure. Over the years, survival after transplantation has improved with advances in both patient management and surgical techniques, but the procedure is not always available in a timely fashion, prompting new surgical approaches such as split-liver transplantation, procurement from living donors, and auxiliary liver transplantation. The problem of organ shortage is compounded by difficulty in predicting the outcome of liver failure. The King’s College prognostic criteria have been adopted by most centers, although they fail to identify patients at low risk of dying. Alternatives to whole organ transplantation for liver dysfunction are under active investigation. Figure 1 schematically depicts the 4 main cellular approaches that are currently being investigated: isolated cell transplantation, tissue engineering of implantable constructs, transgenic xenotransplantation, and extracorporeal bioartificial liver devices (BAL). Extracorporeal support for patients suffering from liver failure has been attempted for over 40 years. Temporary systems have been developed to attempt to expedite recovery from acute decompensation, facilitate regeneration in ALF, or serve as a bridge to liver transplantation. Various nonbiological approaches have met with limited success, presumably because of the role of the synthetic and metabolic functions of the liver that are inadequately replaced in these systems. Hemodialysis, hemoperfusion over charcoal or resin or immobilized enzymes, plasmapheresis, and plasma exchange have all been explored. Conversely, purely biological approaches have shown encouraging results in some cases but have been difficult to implement in the clinical setting. In addition to orthotopic liver transplantation, these include whole organ perfusion, perfusion of liver slices, and cross hemodiafiltration.

Bioartificial devices typically incorporate isolated cells into bioreactors to simultaneously promote cell survival and function as well as provide for a level of transport seen in vivo. Several previous reviews have addressed the field of BAL development. We will highlight recent advances in liver biology and bioengineering that have impacted the field. The important issues include choice of cellular components, stabilization of hepatocyte phenotype, bioreactor design, regulation and safety, and clinical trials.

CELLULAR COMPONENT OF BIOARTIFICIAL LIVER DEVICES

The full complement of cellular functions required in BAL devices to effect positive clinical outcomes has not been determined. To address this problem, surrogate markers of each class of liver-specific functions typically are characterized including: synthetic, metabolic, detoxification (phase I and II pathways), and biliary excretion. The implicit assumption is that hepatocytes capable of a wide array of known functions will also express those unmeasured (or unknown) functions that are central to their metabolic role. Table 1 describes cell types that have been used and are currently being evaluated for use in BAL. Each of these—primary hepatocytes, cell lines, and stem cells—should be evaluated on the basis of availability, potential adverse interactions, and efficacy in providing liver-specific function.

Primary porcine hepatocytes are most commonly used in devices undergoing preclinical and clinical evaluation. Studies have also been conducted with cells isolated from rabbit, canine, and rodent species. There is relatively limited information on the maintenance of liver-specific functions of porcine hepatocytes in vitro. Although some functions such as albumin secretion may be stable, others such as cytochrome P450 decline under standard culture conditions. In general, primary hepatocytes are well known to require specific microenvironmental cues to maintain the hepatic phenotype in vitro, and it is likely that a more detailed investigation of culture conditions will improve the stability of porcine hepatocytes in vitro as has been the case for rodent hepatocytes.

Primary human cells would be ideal, but like whole organs, they are in limited supply. They have been used for BAL application (Gerlach et al., personal communication) as well as for hepatocyte transplantation. A persistent paradox of human hepatocytes is their facile proliferation in vivo but static nature in culture, despite significant progress in stimulating DNA synthesis of rodent hepatocytes in culture. Recent reports regarding underlying differences in telomerase expression in humans and rodents may play a role in this phenomenon.

The growth limitations of primary cells has spurred attempts to develop cell lines that can proliferate in culture while maintaining liver-specific functions. Many cell lines have been established by retroviral transduction or lipofection of the simian virus 40 tumor antigen gene (SV40Tag) whose gene product binds to cell cycle regulator proteins Rb and p53. Spontaneous immortalization has been documented as a result of collagen gel sandwich cultures or cocultures. Cell lines derived from hepatic tumors, such as C3A (a subclone of HepG2), have already been used in clinical trials. We have attempted to categorize the function of a variety of cell lines by tabulating markers of synthetic, metabolic, and detoxification (Table 1). The risk of transmitting oncogenic substances or...
STABILIZATION OF PRIMARY HEPATOCYTE PHENOTYPE

Although primary hepatocytes represent the most direct approach to replacing liver function in hepatic failure, they are anchorage-dependent cells and notoriously difficult to maintain in vitro. When enzymatically isolated from the liver and cultured in monolayer or suspension cultures, they rapidly lose adult liver morphology and differentiated functions. Many investigators have looked to the microstructure of the liver to provide inspiration for culture models that replace the lost cues from the hepatocyte microenvironment in vivo.

Typical approaches involve manipulation of the extracellular matrix environment, media composition, or promotion of cell-cell interaction (both homotypic and heterotypic). Extracellular matrix (ECM) modulation has included both variations in composition and topology.59-66 Sandwich culture63 was designed to mimic the microenvironment of the adult hepatocyte where cells are sandwiched by extracellular matrix in the space of Disse. Cells in this configuration stably express many liver-specific functions; however, attempts to scale-up this culture method have met with limited success thus far.

Modifications such as hormonally defined media55,67 and addition of low concentrations of dimethyl sulfoxide68 or dexamethasone89 are known to help stabilize hepatocyte morphology, survival, and liver-specific functions. However, these approaches are inapplicable to BAL designs because of systemic exposure of patients to these specialized and non-physiologic media components.

Finally, liver-specific functions are stabilized in hepatocytes that are cocultured with nonparenchymal cells (heterotypic interaction—see Bhatia et al.70 for review). Although the precise molecular mechanisms that underlie the coculture effect are not known, it is likely that a highly conserved signaling pathway is involved. Although this concept has not been applied to a clinical BAL device, it merits consideration.

BIOREACTOR DESIGN

Continued innovation in engineering and material science has contributed greatly to the development of extracorporeal liver-assist devices. Coupled with new discoveries in cell sourcing and hepatocyte stabilization, BAL devices tailored for use with hepatocytes are becoming a reality. Table 2 summarizes the bioreactor designs that have been proposed and studied. There are 4 main types, each with inherent advantages and disadvantages: hollow fiber, flat plate and monolayer, perfused beds or scaffolds, and beds with encapsulated or suspended cells. A successful and clinically effective BAL device should satisfy a few key criteria: adequate bidirectional mass transport, maintained cell viability and function, and potential for scale-up to therapeutic levels.

Bidirectional Mass Transfer. In BAL devices, bidirectional mass transfer is needed to provide nutrients to sustain cell viability and allow export of therapeutic cell products. Although most device designs address this, there are important limitations involving the use of membranes, diffusivity of key solutes, and spatial uniformity. Semipermeable membranes provide selectivity for the size of biological molecules that will be exchanged between the patient and the device. They are inherent in hollow fiber devices but have been used also in flat-plate and perfusion systems.71,72 In many hollow fiber devices, the membrane must simultaneously function as a perm-selective barrier and as a scaffold for cell attachment. As noted earlier, the interaction of the hepatocyte with its microenvironment dramatically affects stability and function. Therefore, this design may not allow for optimization of both function and transport. Conversely, hollow fiber designs provide a larger surface-area-to-volume ratio than flat plate designs, thus improving metabolic transport and minimizing dead volume.

The membrane in a BAL device is typically characterized by its molecular weight cutoff, which is selected both to prevent the exposure of bioreactor cells to components of the immune system and to block the transport of larger xenogenic substances into the circulation. The aim of allowing free transport of larger carrier proteins such as albumin (~60 kd) while preventing transport of immunoglobulins (~150 kd), complement (~200 kd), or viruses has led most groups to choose a membrane molecular weight cutoff of 100 to 150 kd. Membranes also prevent the migration of cells into the patient’s circulation, although case reports of cellular translocation exist. While transport in BAL devices is a combination of convective and diffusional phenomena, mass transfer limitations of key nutrients to and from the cellular compartment often arise because of diffusion resistances. In contrast, transport in the liver is achieved primarily by convection along the sinusoid with short diffusion distances (<5 µm) across the space of Disse. Barriers to diffusive transport include membranes,
collagen gels, and nonviable cells. Some designs use encapsulated cells in perfusion systems, which provide immunosolation, but also increases diffusion resistance.\textsuperscript{74-76} Packed bed reactors offer improved mass transfer by allowing direct contact of cells on microcarriers or packing material with the perfusing media.\textsuperscript{36,77-79}

Another aspect of current BAL designs is the universal absence of functional biliary excretion into an isolated compartment. In current configurations, even primary hepatocytes that regain polarity \textit{in vitro} (e.g., spheroids or coculture) excrete biliary constituents into the surrounding fluid, which then recirculate continuously. In this regard, addition of a nonbiological adjunct such as an albumin dialysis module may complement many existing BAL devices. In the long-term, culture environments that promote a separate functional biliary compartment will greatly improve the design of BAL devices.

Oxygenation is key to hepatocyte function and may be suboptimal in current BAL devices.\textsuperscript{80-83} Hollow fiber compartments\textsuperscript{81} or nonwoven fabric scaffolds\textsuperscript{82} with fibers for gas delivery\textsuperscript{83} may improve oxygen delivery. Geometric constraints also may affect mass transport in a BAL. Cell distribution and flow should be uniform. A single monolayer culture is easily perfused, but a series of stacked plates may introduce shunting through regions of low resistance. Hollow fiber devices present difficulty in achieving homogeneous cell distribution during innoculation through the tight matrix of capillaries. Uniform perfusion of packed-bed reactors is a classic engineering problem. Distribution of fluid flow is greatly dependent on the characteristic of the packing material. Larger, rigid particles will yield well-distributed flow but a decreased surface area for cells, whereas smaller, porous packing will result in clogging and fluid channeling.\textsuperscript{86} A packed bed reactor built around a microchanneled scaffold is an example of one designed explicitly to reduce heterogeneous perfusion and improve the transport characteristics of the devices.\textsuperscript{79}

**Cell Viability and Function.** One of the major obstacles to BAL offering long-term treatment is the inability to maintain highly functional hepatocytes \textit{in vitro}. Current device designs do very little to integrate an appropriate microenvironment for hepatocytes. Gel entrapment and use of spheroidal aggregates have been introduced into various membrane-based systems to provide chemical and topological ECM cues or cell-cell interaction; however, this introduces an additional diffusion barrier.\textsuperscript{55,73,79,87-89} Single cell suspensions, used in some devices because of their desirable transport properties, quickly lose metabolic capacity.\textsuperscript{90} Some packed bed designs\textsuperscript{77,78} and one hollow fiber device\textsuperscript{91} seed cells on microcarriers before device assembly. While microcarriers provide

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### Table 1. Cell Sources for Extracorporeal Bioartificial Liver Devices

<table>
<thead>
<tr>
<th>Source</th>
<th>Synthesis</th>
<th>Metabolism</th>
<th>Detoxification</th>
</tr>
</thead>
<tbody>
<tr>
<td>+mAFP, +mAlb</td>
<td>+PK, -urea</td>
<td>-P450</td>
<td>+mUGT1</td>
</tr>
<tr>
<td>+mAFP, +mAlb</td>
<td>+urea</td>
<td>+mGST</td>
<td></td>
</tr>
<tr>
<td>+mAFP, +mG6Pase</td>
<td>+mADH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Derived from blastocyst or germ cells, pluripotent, differentiation to hepatocytes not yet reported \textit{in vitro}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Embryonic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+mAFP, +mAlb</td>
<td>+PK, -urea</td>
<td>-P450</td>
<td>+mUGT1</td>
</tr>
<tr>
<td>+mAFP, +mAlb</td>
<td>+urea</td>
<td>+mGST</td>
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<td>Embryonic</td>
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<td>+mAFP, +mAlb</td>
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<tr>
<td>+mAFP, +mAlb</td>
<td>+urea</td>
<td>+mGST</td>
<td></td>
</tr>
<tr>
<td>+mAFP, +mG6Pase</td>
<td>+mADH</td>
<td></td>
<td></td>
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<tr>
<td>Tumor-derived cells</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HepG2</td>
<td>Hepatoblastoma</td>
<td>+mAFP, +mAlb</td>
<td>+PK, -urea</td>
</tr>
<tr>
<td>C3A</td>
<td>Hepatoblastoma</td>
<td>+mAFP, +mAlb</td>
<td>+PK, -urea</td>
</tr>
<tr>
<td>HuH6, JHH-2</td>
<td>Hepatoblastoma</td>
<td>+mAFP, +mAlb</td>
<td>+PK, -urea</td>
</tr>
<tr>
<td>Potential stem cell sources</td>
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<td></td>
</tr>
<tr>
<td>Embryonic</td>
<td>Derived from blastocyst or germ cells, pluripotent, differentiation to hepatocytes not yet reported \textit{in vitro}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Embryonic</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Progenitor</td>
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<tr>
<td>Transdifferentiated</td>
<td>Pancreas ductal cells induced to hepatic lineage, hematopoietic stem cells produce hepatocytes in liver</td>
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</tbody>
</table>

Abbreviations: +m, mRNA expression; Alb, albumin; NR, not reported; UGT1, UDP-glucuronosyltransferase 1; P450, cytochrome P450; GS, glutamine synthetase; GST, glutathione-S-transferase; -m, low protein secretion; +m, high protein secretion; AFP, \textit{\alpha}-fetoprotein; G6Pase, glucose-6-phosphatase; PK, pyruvate kinase; OCT, ornithine carbamoyltransferase; ADH, alcohol dehydrogenase.

*Basal levels (i.e., noninduced).*
a substrate for anchorage, data from hepatocyte cell culture suggest that these cells will likely detach in a few days and die as they do in monolayers. Along with providing adequate attachment, future devices should consider integrating engineering strategies for efficient transport, environments that optimize cell-ECM interactions and cell-cell interactions, and relevant chemical stimuli.

**Scale-Up.** For a device to become a clinical reality, it must be scaled to a size that provides effective therapy. Studies indicate that between 10% and 30% of normal liver mass is needed to sustain life, which in adults, corresponds to 150 to 450 g of cells. Clinically tested devices incorporate between 1 and 500 g of hepatocyte mass. The current solution for scaling up hollow fiber devices involves increasing cartridge size and using multiple cartridges. Systems using spheroids or microcarriers are easily scaled to the needed cell mass but may entail a considerable dead volume (priming volume). Flat or stacked plate designs raise similar concerns as well as the problem of heterogenous flow distribution and channeling upon scale-up.

**Nonbiological Adjuncts.** Hemoperfusion, in use since the 1960s, removes toxins but also some useful metabolites (growth factors, clotting factors, etc.) from blood circulating through a charcoal column; the column may also activate leukocytes, causing cytokine release. One bioartificial device, the HepatAssist system, which is currently in clinical trials, places a charcoal column before the hollow fiber cell cartridge. Another method called hemodiadsorption minimizes direct contact with charcoal by passing the blood through a flat membrane dialyser containing a suspension of charcoal and exchange resin particles. The BioLogic-DT developed by HemoCleanse is based on this and has been evaluated clinically in patients with ALF. As we shall see later, nonspecific removal of circulating biochemical species has not resulted in a clear survival benefit. The Molecular Adsorbent Recirculating System involves dialysis against charcoal and albumin. The device is more selective than charcoal hemodiadsorption in that it uses a membrane impregnated with albumin to facilitate the clearance of albumin-bound toxins. The device has proven especially effective in reducing blood levels of bilirubin and bile acids in cholestasis and liver failure.
REGULATION AND SAFETY

Because of the hybrid nature of BAL, the regulatory environment has been evolving. Although BALs were originally treated as devices, the biological component of these devices fit the criteria for biologics and the secretory products the criteria for drugs. Current devices are being regulated as drugs through the Center for Biologics and Evaluation Research of the Food and Drug Administration. New guidelines for these and other hybrid devices are being developed by a consensus-based group at the American Society of Testing and Materials in conjunction with other organizations such as the International Standards Organization. Because of their application to ALF patients for whom other therapies do not exist, some devices have undergone fast-track review as orphan drugs. The safety concerns for BAL devices are similar to those for other cellular therapies and include immune reactions to foreign antigens, xenozoonosis, and escape of tumorigenic cells. Antibodies against porcine antigens have been detected in the serum of patients treated with BAL devices, although the clinical impact of this finding is not clear.\textsuperscript{98} High titers are not generated for 1 week (IgM) to 3 weeks (IgG); therefore, immune rejection may play a more significant role in repetitive applications of BAL therapy. BAL devices containing human cells or cell lines may be most appropriate for repetitive clinical treatments, as for patients with chronic liver disease and multiple bouts of acute decompensation. The addition of downstream filters, to guarantee the removal of immortalized cells from the circulating fluid, has been generally accepted as a suitable precautionary measure.

With regard to xenozoonotic infections, studies also have suggested a risk from agents such as PERV,\textsuperscript{73,99,100} which is ubiquitous in the genome of breed pigs. Although PERV has been shown to infect human tissue \textit{in vitro},\textsuperscript{101} 28 patients who underwent treatment with a porcine-based BAL device all tested negative for PERV,\textsuperscript{102} indicating that humans may be nonpermissive for this infection through ALF plasma.

The design of clinical trials for BAL devices has proven to be very challenging for a number of reasons. First, the course of liver failure is variable and etiology dependent. Animal models using hepatotoxins, ischemia, obstruction, or hepatectomy each have had limited predictive ability. Mental-status changes associated with hepatic encephalopathy are difficult to quantify clinically and even less evaluable in animal models. Thus, patients should be randomized to BAL devices while controlling for both the etiology and the stage at which support is initiated. A second difficulty is the choice of the control arm. Typically, patients are randomized against standard medical therapy; however, there are clear differences between extracorporeal perfusion of any kind and noninvasive therapy. For example, there have been anecdotal observations of improvements in hemodynamic stability due to cytokine adsorption on inorganic surfaces in extracorporeal circuits. Similarly, complications caused by catheterization and anticoagulation may bias the clinical outcome. One alternative is to use a nonbiological control such as continuous veno-venous dialysis, which is often used in this patient population in the setting of hepatorenal failure. This would also allow for explicit control over core body temperature during extracorporeal perfusion. This may be particularly important in light of recent data suggesting that hypothermia can decrease intracranial pressure and reduce brain edema. The third difficulty is the choice of the clinical end point. Current trials have used efficacy end points of 30-day survival and 30-day transplantation-free survival. Secondary end points for these studies include improvement in cerebral perfusion pressure, mental status, and encephalopathy stage, in addition to other parameters. The trials are confounded by the fact that ALF patients are transplanted variably but sometimes very quickly, depending on the eligibility criteria of a given center and organ availability. One potential alternative design would be to study 30-day survival and secondary end points in patients who are not transplant candidates and realistically assess the potential of BAL devices to support liver functions.

ONGOING CLINICAL TRIALS FOR EXTRACORPOREAL BIOARTIFICIAL DEVICES

Although no extracorporeal bioartificial liver device has received FDA approval for use in acute or chronic liver failure, a number of clinical trials are underway (Table 3). A difficulty that arises when examining the clinical data is the inability to determine the role of live, functional hepatocytes as opposed to extracorporeal perfusion itself, given that some BAL designs incorporate charcoal filtration. Ideally, a comparison should be made between charcoal filtration alone, dead or nonhepatocyte cells, and live hepatocytes given that nonhepatocyte and dead hepatocytes provided survival benefit in some animal models of ALF.\textsuperscript{103} Also inherent in the present data are a number of practical issues: Are the cells fresh or frozen? Should the device be perfused with plasma or whole blood? What is the role of heparin versus citrate anticoagulation? These issues are critical both for patient well-being and for survival of hepatocytes in the device. The limited function of cryopreserved hepatocytes has been well documented, yet cryopreservation offers flexibility in timing and scheduling of therapies.\textsuperscript{104} The use of whole blood has the advantage of erythrocytes as oxygen-delivery vehicles for BAL, although leukocyte activation and cell damage may occur. Conversely, plasmapheresis and plasma perfusion preserve the viability of hematopoietic cells, yet the solubility of oxygen in plasma is very low. Similarly, heparin anticoagulation has been shown in some studies to cause lipid accumulation and deleterious effects on otherwise phenotypically stable hepatocytes.\textsuperscript{105} Each group has grappled with these trade-offs, and the outcome remains to be seen. Even if these trials do not prove the efficacy of BAL devices, the knowledge gained along with future improvements in cell sourcing and stability will positively impact the next generation of devices.

SUMMARY

In light of the increasing incidence of liver disease and continuing shortage of donor organs, cell-based therapies are gaining attention as promising treatments for liver failure. Currently, several extracorporeal bioartificial liver devices are undergoing clinical evaluation. Their future use will depend on the choice and stabilization of the cellular component. Although cell lines offer a limitless cell source, primary hepatocytes may be preferred because of their broad expression of liver-specific functions. Xenogenic primary cells are available in large quantities, but immunologic and infectious concerns may necessitate the use of human cells or human-derived cells. To improve and maintain functional primary hepatocytes, bioreactor designs must provide architecture that supports cell attachment, cell-cell interaction, cell-matrix interaction, and potential for scale-up. While the safety of BAL devices has been established, there are no uniform standards for the design and evaluation of clinical trials.
of efficacy, which may vary with the etiology of the liver failure. Consensus is needed in clinical trial design, including choice of end points, use of controls, and indications for enrollment. Also, a better understanding of the interplay between liver regeneration and BAL therapy will be critical to optimizing the implementation of this modality.

Acknowledgment: The authors thank Magda Gramada for assistance.

REFERENCES


TABLE 3. Current Clinical Trials of Extracorporeal Support Devices

<table>
<thead>
<tr>
<th>Company</th>
<th>Indication (No. Patients)</th>
<th>% Recovery*</th>
<th>Average Bridge† (hours)</th>
<th>Device</th>
<th>Phase</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biological devices</strong></td>
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</tr>
<tr>
<td>Vitagen (ELAD)</td>
<td>FHF (25)</td>
<td>92% OLT/NR</td>
<td>NA</td>
<td>Sussman et al. 118</td>
<td>I/II</td>
<td>Multicenter C3A cell line, continuous treatment up to 10 days, ultrafiltrate perfusion, 150-300 mL/min, heparin, 4 replaceable cartridges, cell mass: 4 x 200 g 117, 128.</td>
</tr>
<tr>
<td>Hepatix (91-96) (ELAD)</td>
<td>FHF (23)</td>
<td>54% OLT/NR</td>
<td>56</td>
<td>Rozga et al. 92</td>
<td>I/II</td>
<td>Multicenter Cryopreserved porcine, treatment 3-6 h for 1-5 days, 400 mL/min, citrate, charcoal column, centrifugal plasmapheresis, cell mass: 50 g 120, 130.</td>
</tr>
<tr>
<td>Circe Biomedical (HepAssist)</td>
<td>FHF (36)</td>
<td>80% OLT/NR</td>
<td>45</td>
<td>Naugler et al. 119</td>
<td>I</td>
<td>1 Center Primary porcine, whole blood perfusion, heparin anticoagulation, cell mass: 70 g.</td>
</tr>
<tr>
<td>Algenix (LIVERx 2000)</td>
<td>FHF, Grade II</td>
<td>—</td>
<td>—</td>
<td>Nyberg et al. 106</td>
<td>I</td>
<td>1 Center Primary porcine, treatment 6-30 h, whole blood perfusion, heparin anticoagulation cell mass: 100 g.</td>
</tr>
<tr>
<td>Excorp Medical (BLISS)</td>
<td>FHF (2)</td>
<td>50% OLT</td>
<td>33% OLT</td>
<td>Patter et al. 102</td>
<td>I</td>
<td>1 Center Primary porcine, continuous treatment up to 3 days, filtration plasmapheresis, 100 mL/min, heparin anticoagulation, cell mass: 500 g.</td>
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<tr>
<td>Charlie Virchow Clinic-Berlin (MELS)</td>
<td>FHF (8)</td>
<td>100% OLT</td>
<td>27</td>
<td>Gerlach et al. 81</td>
<td>I/II</td>
<td>Multicenter Primary porcine, continuous treatment up to 3 days, filtration plasmapheresis, 100 mL/min, heparin anticoagulation, cell mass: 500 g.</td>
</tr>
<tr>
<td><strong>Nonbiological devices</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Teraklin (MARS)</td>
<td>AOC (64)</td>
<td>~70% OLT/NR</td>
<td>NA</td>
<td>Stange et al. 97</td>
<td>I/II</td>
<td>CE-approved multicenter Dialysis against recycle albumin, 6-h treatments over 2-14 days, heparin anticoagulation 131, 132.</td>
</tr>
<tr>
<td>HemoTherapies (BioLogic-DT)</td>
<td>FHF (39)</td>
<td>56% OLT/NR</td>
<td>77% OLT</td>
<td>Ash et al. 133</td>
<td>FDA-approved multicenter Dialysis against charcoal suspension, treatment 2-6 h for 2-5 consecutive days, 200-250 mL/min, heparin anticoagulation 133.</td>
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</tr>
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Abbreviations: FHF, fulminant hepatic failure; OLT, orthotopic liver transplantation; NR, native recovery; NA, not available; AoC, acute on chronic; PNF, primary nonfunction.

*Percent survival with OLT or without.
†Time between initial treatment and OLT.


