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REVIEW

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From portable dialysis to a bioengineered kidney

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ABSTRACT

Introduction: Since the advent of peritoneal dialysis (PD) in the 1970s, the principles of dialysis have changed little. In the coming decades, several major breakthroughs are expected.

Areas covered: Novel wearable and portable dialysis devices for both hemodialysis (HD) and PD are expected first. The HD devices could facilitate more frequent and longer dialysis outside of the hospital, while improving patient's mobility and autonomy. The PD devices could enhance blood purification and increase technique survival of PD. Further away from clinical application is the bioartificial kidney, containing renal cells. Initially, the bioartificial kidney could be applied for extracorporeal treatment, to partly replace renal tubular endocrine, metabolic, immunoregulatory and secretory functions. Subsequently, intracorporeal treatment may become possible.

Expert commentary: Key factors for successful implementation of miniature dialysis devices are patient attitudes and cost-effectiveness. A well-functioning and safe extracorporeal blood circuit is required for HD. For PD, a double lumen PD catheter would optimize performance. Future research should focus on further miniaturization of the urea removal strategy. For the bio-artificial kidney (BAK), cost effectiveness should be determined and a general set of functional requirements should be defined for future studies. For intracorporeal application, water reabsorption will become a major challenge.

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Bioartificial kidney; wearable artificial kidney; protein bound uremic toxins; implantable artificial kidney; renal replacement therapy

1. Introduction

Worldwide, approximately 3 million patients receive dialysis treatment [1]. The best solution for patients with end-stage kidney disease (ESKD) is kidney transplantation. However, the supply of viable organs cannot cope with current demand [2]. This shortage is expected to worsen with the growing elderly, diabetic, and metabolic syndrome patient populations [3]. Besides kidney transplantation, long-term chronic dialysis, either hemodialysis (HD) or peritoneal dialysis (PD), has become an anchor renal replacement therapy (RRT). However, although life sustaining, existing dialysis techniques are a poor substitute of normal kidney function. They partially compensate for renal glomerular filtration and correct fluid and electrolyte imbalances, but fail to replace the complex renal tubular function: the endocrine, metabolic and secretory activities. While small (<500 Da) water-soluble waste solutes (i.e. uremic toxins) are relatively effectively removed, middle molecules and protein-bound uremic toxin (PBUT) are retained due to the limited pore size of low- and high-flux dialyzers. Only the free fraction of PBUT is available for diffusion across the dialyzer. Clearance of uremic toxins with conventional HD (CHD) is also low because of the discontinuous character of treatment (typically three sessions of 4 h per week) compared with the continuous mode of action of healthy kidneys (168 h per week). As a result, fluid and uremic toxins accumulate during the interdialytic interval, followed by rapid shifts in fluid balance and uremic toxin and electrolyte concentrations during dialysis. This is in sharp contrast with homeostasis maintained by healthy kidneys. More continuous dialysis is provided by PD, that is based on diffusion of toxins and osmosis of excess water from the blood across the peritoneal membrane into dialysate in the abdominal cavity, which is exchanged 4–6 times per day via an abdominal catheter (either manually during the day or automatically by a machine at night [automated PD [APD]]). However, blood clearance is relatively low because the toxin concentration gradient between blood and dialysate rapidly decreases during a dwell which limits solute transport. Other disadvantages of PD are time-consuming exchange procedures during the day or preparation of the APD equipment in the evening and limited technique survival (median 3.7 years [4]). The latter is due to high incidence of recurrent peritonitis and deterioration of the peritoneal membrane as a result of exposure to very high glucose concentrations in the dialysate used to induce osmotic water removal [5]. The inadequacy of conventional dialysis treatment results in poor clinical outcomes, high mortality and low quality of life.

To improve the situation of dialysis patients, novel RRTs are under development (Figure 1). The utilization of emerging

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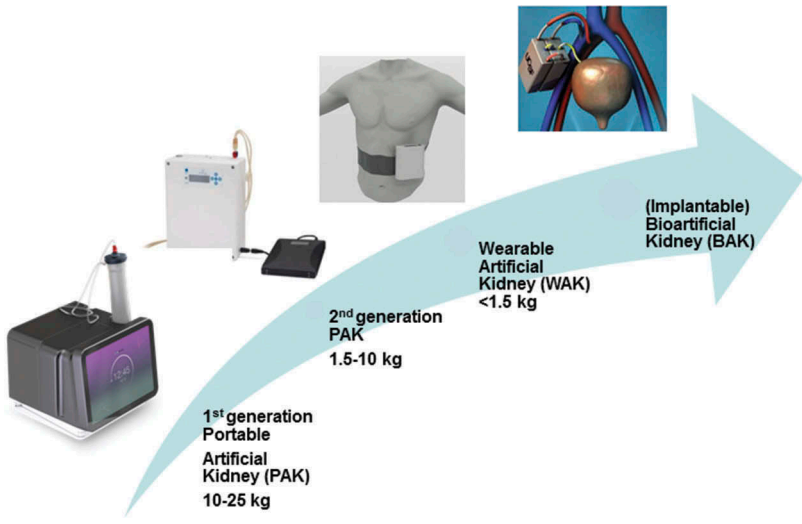

Figure 1. Roadmap toward development of novel renal replacement therapies. 1st generation PAK image courtesy of Neokidney. Implantable BAK image courtesy of dr. Shuvo Roy, UCSF.

disciplines, such as microfluidics and nanotechnology, has led to the development of sophisticated new devices and equipment that challenge the current dialysis treatment paradigms, as devices become smaller, lighter, and are intended for use outside the clinic. The improvement closest to clinical introduction could be offered by a miniaturized dialysis machine. The first generation of dialysis devices will be portable, or rather transportable (weight: ~10–25 kg), intended to be used during sedentary activities or as a bedside device. Further miniaturization may allow for the creation of a wearable device (weight: <1.5 kg), that can be worn on the body during the day. Such portable artificial kidney (PAK) or wearable artificial kidney (WAK) devices can be used at home and during travel, enhancing patient's freedom and autonomy and facilitating participation in economic and social activities, while reducing healthcare costs. PAK and WAK devices can facilitate longer and more frequent RRT, providing patients with less fluctuations in fluid status and internal environment, and possibly improved blood clearance. This may improve clinical outcomes, including survival and quality of life, as observed in observational studies with more frequent and/or prolonged HD [6–8]. However, PAK and WAK devices, like conventional RRT, fail to replace tubular functions, and accordingly, should be considered to be partial substitutive therapies. To address this, strategies are being explored to build an on-demand functional kidney [9–14]. The development of such a bioartificial kidney (BAK), combining synthetic materials with specialized renal epithelial cells, partially replacing tubular function, to be used in combination with standard HD, incorporated in a PAK or WAK or as an implantable device, is making progress. A final goal would be to fully replace kidney function by organ repair or (re)generation.

The aim of this review is to give an overview of novel RRTs that are expected to reach the stage of clinical application within decades and discuss the current status of their development. Focus will first be on miniature devices for HD and PD and subsequently on the BAK. For this purpose, a comprehensive literature search was performed using combinations of the following keywords (including synonyms, abbreviations, and different spellings): HD, PD, portable, wearable, implantable, (bio)artificial, bioengineered kidney, renal assist device (RAD), renal cell therapy (RCT), and PBUT. More futuristic approaches, including recellularization of decellularized kidney scaffolds and kidney organoids for therapeutic application, are beyond the scope of this review.

2. Miniaturization of dialysis machines

2.1. Technical requirements

Efficient water utilization is an important challenge for achieving a portable or wearable dialysis device. Current therapies are characterized by high water consumption. With HD, approximately 280–500 L of water is used to generate 120 L of dialysate per 4-h treatment (dialysate flow of 500 mL/min), depending on efficiency of reverse osmosis [15]. In addition, water treatment systems for HD are stationary and demand high-maintenance and home adaptations to meet specific plumbing and electricity requirements. PD patients use 8–12 L of bagged dialysis fluid per day which also hampers their mobility.

Portable and wearable dialysis devices are based on continuous regeneration of a small volume of spent dialysate by a purification unit in a closed-loop system, independent of a fixed water-source. Current purification units make use of cation and anion exchangers for the removal of potassium and phosphate, respectively, and activated carbon for the removal of organic waste solutes (e.g. creatinine and middle molecules). Urea removal from spent dialysate is difficult because of its hydrophilic character and low reactivity, but this is essential for dialysate regeneration. Although urea is generally considered biologically inert, chronically elevated urea concentrations >20 mM (as commonly observed in dialysis patients) are associated with toxicity caused by the direct effects of urea or by urea-derived (iso)cyanate and ammonia (e.g. urea-/isocyanate-induced carbamylation of proteins and peptides) [16].

Several urea removal methods are available: (1) urease, an enzyme that catalyzes hydrolysis of urea into ammonium and carbonate, was applied in the Recirculating DialYsis (REDY) sorbent system. The REDY system was widely used for dialysate regeneration in HD in the 1970s and 1980s [17,18] but was withdrawn from clinical practice due to inferior treatment adequacy as a result of limited dialysate flow rates (max. 250 mL/min), reports of aluminum toxicity (i.e. osteomalacia and dementia), spillover acidosis, concerns about the release of zirconium and non-cost competitiveness [19–24]. Redesign of the REDY system has eliminated the risk of aluminum toxicity by replacement with a non-aluminum urease immobilization substrate. Remaining disadvantages are ammonium generation requiring binding by a cation exchanger, simultaneous binding of calcium, magnesium and (too much) potassium by the cation exchanger and release of sodium and hydrogen in exchange for bound cations. This necessitates replenishment of calcium, magnesium and potassium, and a system to prevent sodium release to the patient (the released hydrogen is neutralized by the urease-generated bicarbonate). (2) A relatively large quantity of activated carbon (~2–5 kg) can be used to remove the daily urea production (230–470 mmol/day depending on protein intake) [25–27]), as urea has a low-binding affinity for activated carbon (~0.1 mmol/g) [28]. Other urea removal strategies, all not yet available for clinical use, include (3) electrochemical degradation of urea to carbon dioxide and nitrogen gas [29], and (4) removal by adsorbents (e.g. zeolites, resins, silica, and chitosan) [30,31].

Besides water efficiency, other technical requirements for a WAK include: light weight (ideally <1.5 kg), a miniaturized battery operated pump, ergonomic design and safety mechanisms (e.g. automatic discontinuation of the blood pump in case of fluid leakage or air bubble detection). Remote monitoring systems in home dialysis devices enable close surveillance of patients and treatment parameters outside of the hospital and facilitate remote assistance by the medical team [32]. Similar to conventional therapies, biocompatible materials, including non-clotting membranes, should be used. Over the past 10 years, several initiatives have been undertaken to create smaller, mobile, water-efficient dialysis devices for HD and PD. An overview of these developments is provided below.

2.2. Miniature dialysis devices for hemodialysis

Currently, the smallest machines available for home HD (HHD) weigh 24 kg (Physidia S3, France) [33] or 34 kg (NxStage System One, USA and Europe) [34]. In addition, both systems use substantial dialysate volumes (≥20 L/treatment) provided in premixed dialysate bags or generated by a water filtration system (PureFlow™ SL for NxStage), all together limiting patient mobility. Novel WAK and PAK devices for HD are all based on modified REDY sorbent systems, combined with micropumps to drive blood- and dialysate flow, ultrafiltration, and optionally, infusion of heparin (anticoagulant therapy to prevent clotting), calcium, magnesium and potassium. Until now, the WAK™, introduced by Gura et al., is the only wearable device that was tested in humans [35,36]. The WAK™ and other portable devices developed by NeoKidney, EasyDial, Medtronic and Fresenius are discussed in Table 1.

2.2.1. The WAK™

The WAK™ is attached to a large belt to be worn on the body, although the device weighs 5 kg. A small clinical trial demonstrated that continuous dialysis up to 24 h using a tunneled double-lumen central venous catheter is feasible in patients free to ambulate during treatment [36]. A tunneled catheter passed under the skin from insertion site to exit site, to reduce infection risk and be less prone to dislocation due to ingrowth of fibrous tissue. The double lumen allows for simultaneous in- and outflow of blood. During the clinical trial, the preset ultrafiltration volume was achieved, no serious adverse events occurred and hemodynamic, serum electrolyte and hematologic parameters were stable during treatment. Provided that WAK treatment is performed continuously 24 h/day, time-averaged urea, creatinine, phosphate and β_2-microglobulin clearances would be somewhat higher than those with CHD (i.e. 3 × 4 h/week) (Table 1) [39,40]. However, device-related technical problems, i.e. clotting of the extracorporeal circuit and blood leakage into the dialysate compartment, necessitated discontinuation of treatment in two out of seven patients. Moreover, occurrence of a number of other device deficiencies including elevated dialysate ammonia/-um concentrations, early battery failure, occurrence of gas bubbles in the blood circuit, carbon dioxide gas accumulation in the dialysate circuit, tubing kinking and unreliable blood- and dialysate pump function, required early termination of the trial and device redesign.

2.2.2. Neokidney PAK

In an ongoing collaboration between NeoKidney (initiative of the Dutch Kidney Foundation), Debiotech SA (Lausanne, Switzerland), AWAK Pty Ltd (Singapore and Burbank, CA) and the University Medical Center Utrecht (the Netherlands), a PAK is being developed [41]. Initially, the PAK is intended to provide alternate-day 4-h dialysis treatment, but more flexible treatment schemes are under development (e.g. 6 × 2 h/week and nocturnal). The consortium is preparing a first-in-human clinical trial.

2.2.3. Easydial PAK (Dharma™)

A compact portable device called Dharma™, designed as a roller suitcase, is being developed by EasyDial (US, Italy) [42]. An *in vitro* 2-h HD session, utilizing bovine blood spiked with urea (40 mM) and creatinine (1339 µM), demonstrated a mean urea reduction ratio of 78% and creatinine reduction ratio of 91% [43]. However, considerable sodium release (mean plasma sodium increased with 7.3 mM) in exchange for ammonium adsorption by zirconiumphosphate is a concern [44]. The EasyDial system is not yet approved for clinical trials.

2.2.4. Medtronic PAK

The Medtronic PAK is unique in that it uses (partly) regenerable multi-use sorbent-cartridges, whereas all other systems use disposable single-use sorbent cartridges [45]. The Medtronic sorbent cartridge consists of several compartments with sorbent materials that can be individually detached to allow for regeneration of individual compartments by a regeneration system. The device is under preclinical testing.

Table 1. Characteristics of miniature dialysis devices for hemodialysis.

HD-based devices	Device characteristics *Weight, water source + volume of dialysates per treatment, dimensions*	Key features and status of development	References
The WAK™	5 kg (incl. dialysate)	– Wearable belt – Modified REDY sorbent system *In vivo* (ESKD patients): – Continuous treatment up to 24 h/day using a double-lumen-tunneled CVC – Preset ultrafiltration volume achieved (mean: 1 L per 24 h), patients remained hemodynamically stable – Higher clearance (mL/min)[a] vs. CHD [39,40]: • Urea: 17 vs. 14.5 • Creatinine: 16 vs. 9.3 • Phosphate: 15 vs. 6.9 • β_2MG: 5 vs. 1.1 – Several device-related technical complications require device redesign	[35,36]
NeoKidney PAK	10 kg + 6 L dialysate	– Portable[b] – Modified REDY sorbent system – Awaiting clinical trials	[41]
EasyDial PAK (Dharma™)	6.2 kg + 3.7 L dialysate 52×29×18 cm	– Portable[b] – Modified REDY sorbent system – Awaiting clinical trials *In vitro* (bovine blood spike with urea) – Mean urea and creatinine reduction ratio of 78% and 91%, resp. – Sodium release (mean plasma sodium increased by 7.3 mM)	[43,44]
Medtronic PAK	Unknown	– Modified REDY sorbent system – Possibly regenerable sorbent cartridges – Status of development unknown	[37,38,45]
Fresenius PAK	30 kg + 6 L tap water	– Relatively heavy – Water source: tap water – Modified REDY sorbent system – No recent advances have been made public	[46,47]

β_2MG: β_2-microglobulin; CHD: conventional hemodialysis (3×4 h/week); CVC: central venous catheter; ESKD: end-stage kidney disease; PAK: portable artificial kidney; REDY: Recirculating DialYsis; WAK: wearable artificial kidney.
[a]On condition that utilization of 24 h per day is provided, with a mean blood flow of 42 mL/min.
[b]Portable, i.e. transportable, too heavy to be worn on the body continuously.

2.2.5. Fresenius PAK

The Fresenius PAK has been expected for several years. Although this portable machine is relatively heavy compared with other PAKs, the system uses tap water to generate dialysate, whereas other systems require premixed dialysate [46,47]. No recent advances have been made public.

2.3. Miniature dialysis devices for peritoneal dialysis

The inefficiency of conventional PD is inherent to the 'cyclic dwell' regime with 4–6 exchanges per day, characterized by a rapid decline in solute clearance and osmotic fluid removal during a dwell as a result of rising intraperitoneal dialysate solute concentrations and a declining transmembrane osmotic gradient (due to glucose absorption), respectively.

Novel miniaturized devices in development for PD are based on continuous flow PD (CFPD) with continuous regeneration of the peritoneal dialysate. With this technique, dialysate is continuously recirculated into and out of the peritoneal cavity in a closed-loop system, wherein a purification unit (comprising sorbent technology) regenerates the peritoneal dialysate, instead of performing a static fill and drain as in conventional PD [48]. CFPD has a number of advantages: (1) CFPD increases blood purification 2–9 fold as compared with conventional cyclic dwell PD (depending on dialysate flow rate) [49,50]. This is due to a) a constant high diffusion gradient as a result of continuous refreshment of dialysate and b) a 2.5-fold increase in the mass transfer area coefficient of the peritoneal membrane [49,51], due to the reduction of diffusion resistance, renewal of stagnant fluid layers at the peritoneal membrane surface, and an increase in effective membrane area as a result of continuous flow of fluid [52]. (2) By continuously refreshing dialysate in the abdomen, glucose concentrations can be kept constant at lower levels with CFPD, resulting in (a) maintenance of a constant ultrafiltration rate throughout the entire treatment and (b) avoidance of exposure to high glucose concentrations as applied in conventional PD, which might prevent functional deterioration of the peritoneal membrane. (3) Continuous dialysate regeneration allows reduction in the number of exchanges to 0–1/day, which saves time and may lower peritonitis risk due to less (dis)connections [53]. Thus, CFPD may prolong PD technique survival by preventing exposure of the peritoneal membrane to high glucose concentrations and by lowering peritonitis rate, which both cause functional deterioration of the peritoneal membrane.

CFPD can be achieved via two separate single-lumen catheters or one dual lumen catheter (the latter is not commercially available) [54]. Alternatively, rapid alternate in- and outflow of peritoneal dialysate (tidal PD) can be performed using a single-lumen catheter, although this decreases efficiency. Advances in the field of wearable/portable sorbent-based CFPD systems are discussed in Table 2.

2.3.1. CLS PD

The novel Carry Life System for PD (CLS PD), provided by the Swedish company Triomed *AB*, is intended to be worn on the body and contains ion-exchange resins, one for phosphate and one for potassium removal and activated carbon for urea and organic compounds. Triomed is currently recruiting patients for a first in human trial [56]. During the clinical trial, a temporary catheter will be inserted in addition to patients' existing PD catheter to allow for CFPD. A single 8-h treatment session will be performed, with replacement of the sorbent cartridge after 4 h.

2.3.2. AWAK PD

The Automated WAK for PD (AWAK PD) is a wearable system that comprises a sorbent cartridge based on modified REDY sorbent technology. The system applies a tidal mode of PD, providing 12–16 L of dialysate flow per 6–8 h treatment [57]. Evaluation of the AWAK PD system in a uremic pig model demonstrated effective ultrafiltration (1.3 L/7 h treatment) and urea, creatinine and phosphate clearances that compared favorably to time-averaged clearances achieved with CAPD/APD (Table 2) [39,58]. Phosphate clearance was better than that achieved with CHD [39]. AWAK is currently awaiting clinical trials.

2.3.3. WEAKID

A WEarable Artificial KIDney (WEAKID) has been developed by Nanodialysis BV (Oirschot, the Netherlands) in collaboration with the University Medical Center Utrecht (the Netherlands), Università degli Studi di Modena e Reggio Emilia (UNIMORE, Italy) and SERMAS Instituto de Investigación Hospital Universitario La Paz (IdiPAZ, Spain) as part of the European Union's Horizon 2020 research and innovation program [59]. The WEAKID system comprises a sorbent cartridge containing an ion exchanger and activated carbon and is combined with dialysate during the night. This system is intended to provide 8 h of tidal PD at night using the patient's existing single-lumen PD catheter. Optionally, a wearable device (~1.5 kg), containing a second sorbent cartridge, can provide additional clearance during the day. The consortium is preparing clinical trials.

2.3.4. ViWAK PD

The Vicenza Wearable Artificial Kidney for PD (ViWAK PD) is a system for CFPD. An *in vitro* study, in which 12 L of spent patient peritoneal effluent was circulated through the sorbents, demonstrated efficient creatinine and middle molecule removal as a proof of principle [60]. However, the system, already presented in 2007, was far from finalized, because of the lack of a urea removal system, glucose, and bicarbonate administration systems and a filter to prevent fibrin deposition on the sorbent cartridge. No recent advances have been made public.

3. The bioartificial kidney: approaching the clinics

All of the above-mentioned RRTs fail to replace tubular functions, including active tubular secretion of PBUT [9–11]. One way to achieve this goal is to expand the functionality of conventional therapies by including cellular components capable of taking over tubular functions of the kidney, thus introducing the critical transport, metabolic, and endocrine functions of the kidney (Figure 2)

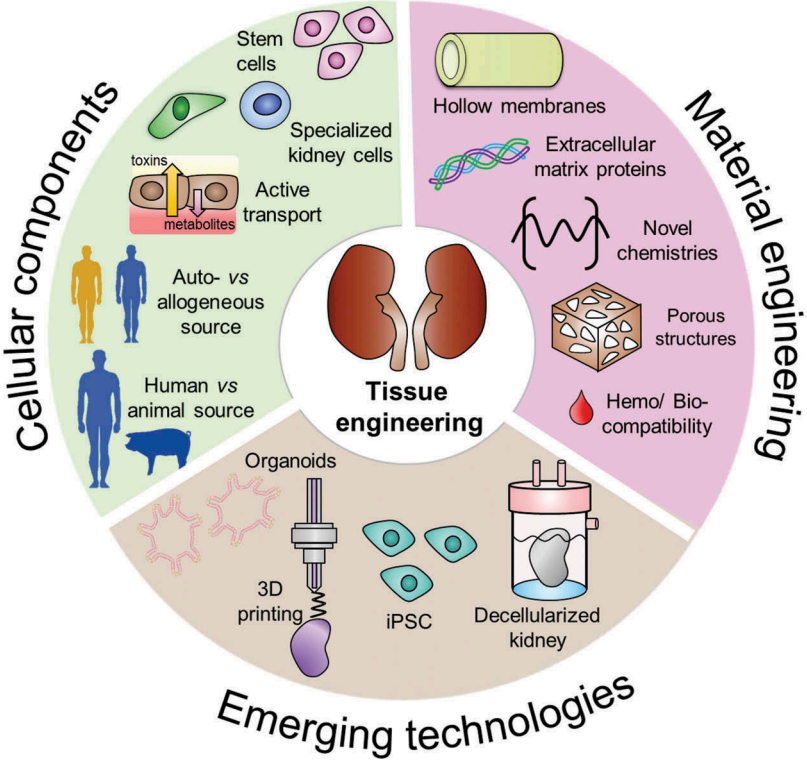

Figure 2. Key features of the development of a bioengineered kidney. Besides specialized kidney cells, additional cell sources and tools have become available, including embryonic stem cells and induced pluripotent stem cells (iPSC), organoids and 3D printing, that enable acquisition of tissue specific functionality. Improved chemistries and use of tissue specific extracellular matrix, as well as advances in understanding biophysical cues on cellular behavior and tissue architecture technologies, could contribute to tissue engineered kidneys with improved structural, compositional and functional resemblance to native counterparts.

Table 2. Characteristics of miniature dialysis devices for peritoneal dialysis.

PD-based devices	Device characteristics *Weight, water source + volume of PD fluid per treatment*	Key features and status of development	References and CT registry
CLS PD	<3 kg + 2.5–3 L PD fluid	– Wearable – Sorbent cartridge: ion exchangers + activated carbon – Cartridge life-time: 4 hCFPD via two single-lumen PD catheters – Intended to provide 8–12 h treatment/day – Battery-powered – Recruiting patients for first in human clinical trial	[56] NCT03190018
AWAK PD	<2 kg + 2 L PD fluid	– Wearable – Modified REDY sorbent system – Tidal PD via patients' existing single-lumen PD catheter (mean dialysate flow rate: ~33 mL/min) *In vivo* (anephric porcine model): – Higher clearance (mL/min)[a] vs. PD [39]: • Urea: 12.3 vs 6.0 • Creatinine: 5.8 vs. 4.3 • Phosphate: 10 vs. 3.2 (higher than with CHD: 6.9)	[57]
WEAKID	~1.5 kg (incl. sorbent cartridge) + dialysate (during night) + 2 L PD fluid	– Wearable – Sorbent cartridge: ion exchangers + activated carbon – Tidal PD via patient's existing single-lumen PD catheter	[59]
ViWAK PD	Weight: unknown 2 L PD fluid	– Wearable – Sorbent cartridge: polystyrenic resin + activated carbon – Intended to provide CFPD for 10 h/day (mean dialysate flow rate: 20 ml/min) – Device not finalized: lack of a urea removal system and glucose and bicarbonate administration systems *In vitro* (circulation of spent peritoneal dialysate): – Higher creatinine clearance (mL/min) vs. PD[a]: 7.8 vs. 4.3 – Higher β_2MG clearance vs. PD and CHD[a]: 7.9 vs. 0.6–1.1	[60 39 40,55]

AWAK PD: automated wearable artificial kidney for peritoneal dialysis; CHD: conventional hemodialysis (3×4 h/week); CLS PD: Cary Life System for peritoneal dialysis; CFPD: continuous flow peritoneal dialysis; CT: clinical trial; ViWAK: Vicenza Wearable Artificial Kidney; WAK: wearable artificial kidney; WEAKID: WEarable Artificial KIDney.
[a]Time-averaged clearance.

[12–14]. In recent years, substantial progress has been made in the development of the BAK (Table 3) [61–67]. Because of the targeted high capacity clearance of PBUT, this approach is expected to result in considerable lowering of PBUT plasma concentrations [68], which may significantly reduce (cardiovascular) morbidity and mortality and increase quality of life [69]. However, before a biocompatible BAK becomes available, several milestones need to be addressed, under strict evaluation of regulatory bodies.

3.1. Complementing dialysis: the renal assist device

The first BAK was developed by Humes and co-workers as an extracorporeal cell-loaded RAD providing metabolic and endocrine functions of the renal tubule, connected in series with a conventional hemofilter providing clearance of primarily non-PBUT (substituting glomerular filtration). The RAD is based on a standard hollow-fiber hemofiltration cartridge loaded with 10^8 to 10^9 human proximal tubule epithelial cell (PTEC) grown along the lumen of hollow-fiber membranes [78–81]. Extensive preclinical studies demonstrated that the RAD possesses multiple transport, metabolic, and endocrine functions representative of kidney tubular epithelium [78,79]. Supported by these promising preclinical data, phase-I and -II clinical trials were conducted in intensive care unit patients with acute kidney injury (AKI) that showed RAD therapy to be safe for use for up to 24 h, with a substantive clinical impact on survival and renal recovery [82,83]. The early clinical success of the RAD as a RRT for patients with AKI propelled a follow-up phase-IIb study to evaluate the commercial manufacturing process for the RAD. Unexpectedly, the device was seen to modulate inflammation, even without living cells [82]. However, the study was discontinued due to lack of both a reliable cell source and technologies to store, deliver and use these units at point of care facilities [84]. Nevertheless, the RAD is still the only BAK-like device that has been successfully tested in humans.

3.2. The wearable BAK: an update on the bioartificial renal epithelial cell system (BRECS)

A breakthrough in overcoming these road-blocks is the bioartificial renal epithelial cell system (BRECS), the first cryopreservable

Table 3. Characteristics of cell-based BAK prototypes using PTECs.

System	Device characteristics *Cell and materials type, configuration, coating, MWCO*	Key features and status of development	References
BTD	– Human PTEC – EVAL hollow-fiber modules *(Asahi Kuraray Medical Co. Ltd)* – Attachin – <65 kDa	*In vitro*: – Wearable – Reabsorption of water, sodium and metabolization of β_2MG and pentosidine *In vivo* (AKI in goats): – Extension of life span, reduced PBMC expression of inflammatory cytokines and plasma IL-6 levels – Expansion in serum free-conditions – No information on PBUT clearance	[70 71 72]
RAD	– Porcine and human PTEC seeded intraluminally – Conventional hemofilter polysulphone hollow fibers with surface areas of either 0.4 m^2 (*Minntech, USA*) or 0.7 m^2 (*Fresenius USA,*) – Pronectin-L coating – 50 kDa	*In vivo* ((endotoxin-challenged) anephric dogs): – Increased ammonia excretion – Confirmed immunoprotection – Active glutathione metabolism, and 1,25-dihydroxyvitamin D3 production *Clinical studies*: – Phase-I/-II trial (AKI and MOF): • Increased survival at day 180 • More rapid renal recovery • No information on PBUT clearance	[73,78,74 82,83]
BAK Living membranes	– Human ciPTEC – PES and MicroPES hollow fibers (*3 M Membrana*) – L-DOPA and human collagen IV – 150 kDa	*In vitro*: – Confirmed secretory clearance/active transport of organic cations and PBUT – Maintenance of barrier function during culture – Confirmed albumin reabsorption across the renal tubule – Absence of direct immunogenic effect of ciPTEC – Upscaling to multiple fiber module	[62,102 75 103]
BRECs	– Human PTEC derived from adult progenitor cells – Trabeculated disks of niobium-coated carbon, held within cryopreservable, perfusable, injection-molded polycarbonate housing – <65 kDa	*In vitro*: – Succesful cryopreservation of all-in-one culture vessel containing cells – Confirmed immuneprotection – Conversion of 25-hydroxyvitamin D3 to 1,25-dihydroxyvitamin D3 *In vivo* (porcine model of septic shock): – Prolonged survival through stabilization of cardiac output and vascular leak *In vivo* (anephric sheep): – Wearable design – Confirmed immuneprotection – Conversion of 25-hydroxyvitamin D3 to 1,25-dihydroxyvitamin D3 – Peritoneal dialysis fluid is used to support the biological device and delivery of cell therapy while providing uremic control – Retained neutrophil oxidative activity (better than sham) – No information on PBUT clearance – Awaiting clinical trials	[85 88 88 67]
BAK	– Human PTEC seeded extraluminally – PAES (Gambro Singapore) – PSU (Frenesius Medical Care, the Netherlands) – PES/PVP self-made hollow-fiber membranes – L-DOPA and human collagen IV – <65 kDa	*In vitro*: – Organic anion transport – Release of IL-6 and IL-8 – No follow-up reports after 2013	[76,77]

AKI: acute kidney injury; BAK: bioartificial kidney; BTD: bioartificial renal tubule devices; β_2MG: β_2-microglobulin; ciPTECs: conditionally immortalized proximal tubule epithelial cells; EVAL: ethylene vinyl alcohol; FDA: Food and Drug Administration; IL: interleukin; KHI: Kidney Health Initiative; L-DOPA: L-3,4-dihydroxyphenylalanine; MOF: multiorgan failure; MWCO: molecular weigth cut-off; PAES: polyarylethersulfone; PBMC: peripheral blood mononuclear cell; PBUT: protein-bound uremic toxins; PES/PVP: polyethersulfone/polyvinylpyrrolidone; PSU: polysulfone PTEC: proximal tubule epithelial cells.

cell therapy delivery system designed as an all-in-one culture vessel containing cells [85]. The BRECS enables mass biofabrication, storage and distribution, all features that are attractive for clinical settings. Based on the same concept as the RAD, the BRECS utilizes a similar renal progenitor cell population differentiated toward renal epithelial phenotype. Prior to therapeutic application, primary cells are expanded in a perfusion bioreactor. Cells are maintained at high density on porous disks, placed within a medium flow path [2,85–87]. Subsequently, the BRECS is cryopreserved, and upon reconstitution 1–3 months later, the cells retain their viability, kidney cell-specific metabolic functions, as well as specific renal epithelial differentiation markers, suggesting that BRECS could provide kidney tubular cell-specific metabolic supplementation to conventional RRT on demand

[85,88]. Thus, BRECS could allow long-term storage and clinical application in an 'off-the-shelf' formulation. Further developments in manufacturing of BRECS now allow fast production of housing units at low costs [89].

Following the same translational route as the RAD, BRECS was tested in large animals to determine safety profile and potential efficacy. In a porcine model of septic shock, intraperitoneal administration of high-dose *Escherichia coli* resulted in a rapid fall in blood pressure and concomitant reduction in vital organ function [88]. Without intervention (i.e. with acellular sham devices), death occurred within 8 h. In contrast, insertion of BRECS into the ultrafiltrate biofeedback component of an extracorporeal circuit conveyed a significant survival advantage over acellular controls, extending mean survival time to 13 h. Prolonged survival may have been due to active involvement of BRECS in stabilization of cardiac performance and reduction of vascular leakage. These results are important in bringing RCT closer to clinical application.

For HD, however, development of RCT faces a number of limitations, among which most poignant is related to maintenance of an extracorporeal blood circuit without thrombosis. Thus, elimination of a blood circuit, an inherent characteristic of HD-based therapy, would facilitate its development. One approach being explored is a wearable bioartificial kidney (WeBAK) for PD, a type of BRECS that uses peritoneal dialysate to provide oxygen and nutrients to the cells [67]. For uremic control sorbent technology is applied to regenerate the peritoneal dialysate, which is subsequently perfused through the BRECS, providing tubular cell functions [67]. The WeBAK was tested in a large animal model. Anephric sheep were treated with CFPD, that included a BRECS in the peritoneal dialysate regeneration circuit or an acellular (sham) device, for up to 7 days, during which metabolic, endocrinological and immunological parameters were monitored. Cell viability and metabolic activity were sustained via the extracorporeal peritoneal fluid circulation. Furthermore, a systemic immunological effect of BRECS therapy was observed as cell-treated sheep retained neutrophil oxidative activity better than sham-treated animals [67]. This study highlights potential use of a WeBAK, without the constraints of an anticoagulated blood circuit, to provide RCT for ESKD.

According to Innovative BioTherapies, Inc., the company developing the BRECS, preclinical trials for both acute (AKI) and chronic (ESKD) therapeutic applications, followed by human trials are expected [90].

3.3. Emerging technologies for the removal of protein-bound uremic toxins

Although BRECS technology assures metabolic and endocrine function in combination with an immunoprotected filtration system, a very important feature of the kidneys discussed in the introduction seems missing: removal of PBUT.

Several methods to increase PBUT removal have been explored: (1) Extending dialysis sessions and increasing the dialyzer mass transfer area coefficient and dialysate flow rate improve removal of PBUT only to a limited extent [7,91,92]. (2) Pre-dialyzer infusion of PBUT-binding competitors (tryptophan, ibuprofen and furosemide) increase PBUT removal *in vitro* (1.4- and 2.9-fold increase of indoxyl sulfate (IS) removal and 1.3- and 2.1-fold increase of indoleactic acid removal by infusion of tryptophan or a combination of ibuprofen and furosemide, respectively) [93]. However, to achieve removal of a broad spectrum of PBUT, several PBUT-binding competitors should be infused, taking into account clinically acceptable plasma concentrations. Studies are ongoing to find the ideal-binding competitors that are both efficacious and safe for long term routine clinical use. (3) So-called hollow-fiber mixed-matrix membrane (MMM), that combine on and adsorption into one membrane proved to be efficient in removal of the pre-dialysis free fraction [94,95]. MMM consist of two layers: an outer layer with adsorptive particles (e.g. activated carbon) incorporated in a porous polymer and a particle-free hemocompatible inner membrane. The diffused free fraction is continuously adsorbed, thus maintaining a high concentration gradient across the dialyzer that drives diffusion. However, PBUT removal by MMM is limited by the fact that only the free faction can pass the filter and the pre-dialysis protein-bound/free fraction equilibrium is not completely restored during the treatment (the percentage protein binding increases) [96]. 4) Hypertonic predilution hemodiafiltration is a technique that infuses hypertonic saline into pre-filter replacement fluid to enhance plasma ionic strength (HDF-IPIS), stimulating release of toxins from proteins, thus making them available for clearance through filtration [97,98]. HDF-IPIS was shown to increase clearance of the free-fraction of IS by 1.4-fold compared with HD in humans [97]. 5) Hemodiafiltration with endogenous reinfusion (HFR) combining convection, adsorption and diffusion using a double-chamber system improved p-cresol removal. The ultrafiltrate, containing small amounts of albumin generated in the first chamber via a high-flux filter (sieving coefficient for albumin of 0.02), passes through a resin cartridge for PBUT removal, and is reinfused into the blood that subsequently enters a second chamber for diffusive removal via a low-flux filter [99]. 6) Combined fractionated plasma separation and adsorption, was shown to increase PBUT removal (1.3-fold increase for phenylacetic acid and p-cresol removal and 1.9-fold for IS). With this technique, plasma is separated and passed over two hydrophobic and cationic adsorbers for PBUT removal, followed by plasma reinfusion into the blood circuit and passage through a high-flux dialyzer [100].

3.4. Bioengineered living membranes capable of transport of uremic toxins

Despite innovative technological advancements, most of the strategies presented above are still bound to limitations of CHD. All of these, except for combined plasma separation and adsorption, merely enhance availability of PBUT' free fractions. Engineering technologies that recapitulate the endogeneous capacity of kidneys to process PBUT would substantially boost efforts to obtain a fully functional BAK. Since PTEC mediate renal excretion of PBUT via active transport processes, these cells hold clues to develop these

technologies. Recently our group developed a cell line, the human conditionally immortalized PTEC (ciPTEC), enriched in organic in- and efflux transporters, specific for PBUT handling [101]. Culturing these cells on commercially available hollow fibers, commonly used in HD, ensured formation of a polarized leakproof cell monolayer, essential for compartmentalized transport. For the first time, the transepithelial clearance of protein-bound IS and kynurenic acid, both prototypical PBUT, was demonstrated across polarized ciPTEC coated hollow fibers, or bioengineered living membranes [61,62,102]. When upscaling from one fiber to a multifiber module, these features were maintained [103]. Noteworthy, in the presence of albumin, clearance capacity was highly increased, emphasizing the role of albumin in stimulating and sustaining active transport processes [62,104]. Studies on continuous perfusion of cell-coated fiber modules with uremic plasma are currently ongoing, making *in vivo* validation feasible in the future. Combined with a conventional hemodialyzer, providing diffusive transport of non-PBUT, coupled in series with our living membranes upscaled system, replicating the tubular functions of the kidney, we envision RRT of superior performance (Figure 3).

3.5. Toward an implantable renal assist device (iRAD)

Further miniaturization of the in-series coupling of a hemofilter with a cell bioreactor, or RAD, led to the development by Fissel and Roy of a prototype model for a first implantable BAK, in an attempt to eliminate the need for dialysis [105,106]. The implantable renal assist device (iRAD) utilizes microelectromechanical system (MEMS) technology to scale down the original RAD design into a compact, implantable and self-sustainable BAK. The iRAD combines a long-life hemofilter made of silicon nanopore membrane (SNM) with a renal tubule cell bioreactor, such as the BRECS, with immune-isolation properties [107–111]. The slit-shaped pore design of SNM renders pore sizes as small as 5 nm, closely resembling the glomerular function barrier. This feature renders SNM to selectively filter solutes based on a molecular weight cut-off. A greater selectivity of SNM compared with the standard hemofilter membranes has been shown *in vitro* using various globular proteins [108,112]. The miniaturization capabilities inherent to MEMS technology allow for a total surface area of 0.1 m^2 for the device. The long-term stability of hemofiltration was demonstrated for almost 100 h of continuous *in vitro* filtration using anticoagulated blood. With the high permeability of the SNM it is possible to rely on the arterial-venous pressure difference alone, without the use of an additional pump, tethers or immunosuppressant drugs [113–115]. A small pilot study in dogs showed that the hemofilter remained unclotted, while the silicon membranes remained intact, without albumin leakage, for a period of 8 days [112]. Additional testing is needed to determine optimal membrane characteristics and identify limiting factors in long-term implantation. The major achievement of SNM will be determined by their capacity to minimize loss of essential macromolecules, while maximizing uremic toxin and water permeability. One major challenge for iRAD will be reabsorption of water from filtrate since for clinically relevant clearance of small water-soluble uremic toxins at least 15 L of filtrate needs to be produced daily. The Kidney Project, led by Shuvo Roy, is raising funds for a first-in-human trial.

4. Efforts to accelerate the clinical translation of new renal replacement therapies

Recognizing the need for clinical trials and the unmet medical needs of patient with kidney failure, the American Society of Nephrology and the US Food and Drug Administration (FDA) established the Kidney Health Initiative (KHI) in 2002 under a Memorandum of Understanding [116–118]. The KHI, a public–private partnership, is designed to establish a collaborative environment for all stakeholders in the kidney community (academics, patient organizations, regulators, industry, healthcare providers, foundations, pharmaceutical and biotechnological companies, dialysis providers, and US and international governamental agencies) to interact and help foster development of innovative therapies for kidney diseases [116]. By adopting a proactive approach, KHI intends to facilitate availability of the right drug, device or biologic to the right patient at the right time [119,120]. Also non-US stakeholders participate in the KHI, including the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA), the Dutch Kidney Foundation, the Institute Kidney Foundation of Delhi and Frenesius Medical Care (Germany), world's largest dialysis provider. In addition, the FDA has selected two renal device projects, in 2012 the Kidney Project and in 2015 the WAK, to participate in a new regulatory approval program (Expedited Access Pathway, EAP) that intends to speed-up the process of bringing breakthrough medical device technologies to patients [105,118,121–123].

5. Conclusions

Currently, several suitcase-size, portable and wearable cell-free dialysis machines are being developed and moving toward clinical application. Although they will represent a major step forward for dialysis patients, facilitating home dialysis and providing patients with more flexibility and autonomy, cell-based therapies such as the BAK and iRAD have the potential to truly wean ESKD patients from the heavy challenges of dialysis shortcomings, providing them with a sense of normality. A fully functional bioartificial or bioengineered kidney capable of reproducing the metabolic, endocrine, immunomodulatory, and secretory functions of native kidneys could, in the long run, be considered a clinically viable option.

6. Expert commentary

Several key factors are important for successful implementation of miniaturized dialysis devices into the clinic. First, (continuous) HD with a wearable device is cumbered by the need for maintenance of anticoagulation therapy, and risks associated with the extracorporeal blood circuit, including infection, clotting and bleeding events due to needle or catheter dislodgement which may be more likely to occur if patients are mobile during treatment. Thus, establishing optimal

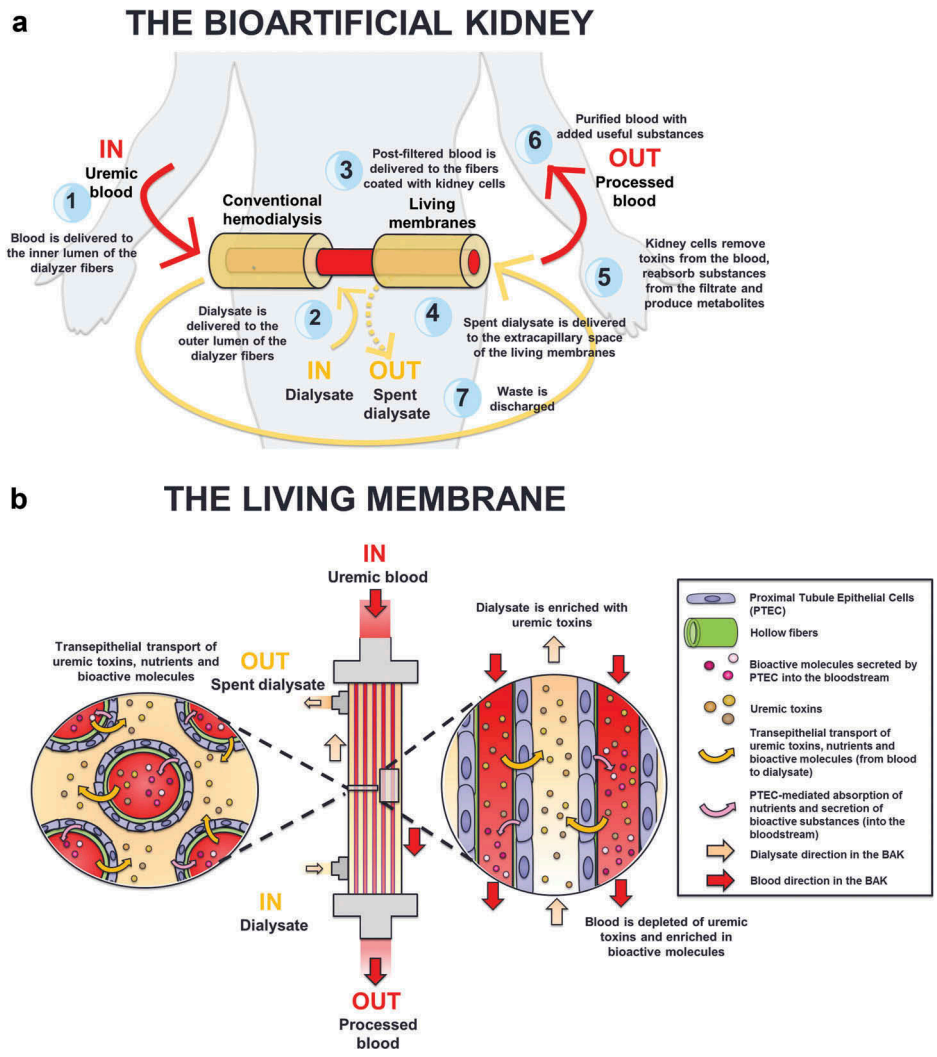

Figure 3. The bioartficial kidney principle. (a) Schema of a BAK prototype. A conventional hemofilter is coupled in series with a cell bioreactor comprising a hollow fiber coated on the extraluminal side with kidney cells. (b) The living membrane of the BAK consists of human proximal tubule epithelial cells (PTEC) cultured on hollow membranes. These cells are capable of active transport of uremic toxins and nutrients and secretion of bioactive molecules.

dosing requirements for anticoagulation and a secure well-functioning vascular access are essential. Second, patients need to be willing to adopt HHD, while a lack of patient motivation is a frequently reported barrier to start HHD. Possibly, reluctance to being identifiable as a patient or the inconvenience of carrying a device might prevent patients from adopting treatment with a WAK. Addressing these barriers during patient education programs is therefore crucial. Third, costs of WAK and PAK devices might exceed those of conventional dialysis during the first years. However, improved clinical outcomes resulting from prolonged dialysis in the home environment might render WAK and PAK devices a cost-effective treatment on the long term. This will also depend on the level of self-management that can be achieved, as home medical staff is expensive. Future research regarding miniature dialysis devices should focus on further miniaturization since the current 'wearable' devices are either still rather bulky (WAK^{TM}; 5 kg) or need several cartridges per day, resulting in a still considerable total weight of materials used per day (CLS PD and AWAK PD). One of the most important challenges in this regard is further rminiaturization of the urea removal strategy. A urea sorbent that can specifically and efficiently bind urea would be ideal. With regard to the PD devices, a future optimization step could include the development of a double-lumen PD catheter that will further enhance efficiency of CFPD compared with tidal PD, due to higher dialysate flow rates and less recirculation.

With regard to the BAK, the critical building blocks are advancing. With recent developments in cryoperservation of cell-loaded devices, the remote manufacturing, storage, and distribution of BAK systems is a reality. However, before clinical implementation, BAK devices require further research to investigate efficacy of the cell and scaffolding systems. Furthermore, there is a lack of uniform readout parameters to describe BAK systems performance in general. Thus, we suggest that future studies should address the following functional requirements: (1) membrane characteristics: material type, porosity, additional coatings or modifications, sieving coefficient, (2) cell characteristics: source, phenotype, genetic modification, passage number, culture conditions, and (3) renal functional aspects, i.e.

active PBUT excretion, ion transport, vitamin D activation, immunogenic effect, and nutrient reabsorption capacity. For an implantable artificial kidney, water reabsorption will become a major challenge as ~90% of filtrate must be reabsorbed at a minimal filtration rate of 10–15 mL/min which amounts to 13–19 L of water per day. Inducing overexpression of water channels (aquaporin 1) by tubular cells may help to solve this problem, although it is still unclear how an osmotic gradient required for water permeation can be generated [124,125].

Of the discussed BAK systems, iRAD is expected to reach clinical trials first. Aim of the Kidney Project is to have completed clinical trials by 2020. However, we doubt whether this goal is realistic. Until now, the project has been fraught with financial and regulatory barriers. In addition, most reported studies on the iRAD primarily refer to technological aspects related to miniaturization and it remains unclear to what extent iRAD replaces kidney function, impeding an estimation of its therapeutic potential. The recent proactive attitude and support of governmental bodies, healthcare policy-markers and funding and regulatory agencies will advance its development.

At this stage, the high costs of on demand production and storage of the cell-loaded BAK devices, are a barrier for implementation for maintenance dialysis, although for AKI, BAK treatment for a limited period of time might be feasible. Eventually, if costs of production can be reduced, BAK-based RCT might be a cost-effective treatment resulting in improved health outcomes and quality of life compared with conventional dialysis.

7. Five-year view

Within the near future, several WAK and PAK devices for HD and PD are expected to enter the phase of clinical testing. The first devices that will be introduced into the market will be portable, but several wearable initiatives, in particular for PD, are at an advanced stage of development and are expected to be ready for clinical implementation soon thereafter.

Regarding BAK devices, important milestones have been achieved. Of the discussed systems, iRAD is expected to be the first to reach clinical trials.

In parallel, tissue engineering-driven approaches have gained substantial interest from the reseach community as an opportunity to advance the replication of architectural and compositional features of the kidney in addition to function. In this direction, '"kidney-shaped"' scaffolds have been developed, that provide a structural support with bioinstructive molecules upon which cells are seeded. In addition, the organ itself could be used as a scaffold by removing the cellular components and maintaining the intricate internal organization and extracellular matrix composition. Repopulating these scaffolds with cells (adult stem cells, induced pluripotent stem cells, kidney organoids, kidney primary cells, etc.) is expected to replicate cellular complexity of the tissue. Future studies should focus on providing appropriate conditions for these cells to develop functional renal tissue. Thus, tissue-engineered approaches are on the rise, but still far away from clinical applicability.

Key issues

- Wearable (WAK) and portable (PAK) devices for HD and PD are based on continuous regeneration of a small volume of dialysate by a purification unit, including sorbent technology, in a closed-loop system, independent of a fixed water-source.
- A miniature dialysis device offers improved freedom and autonomy in the home environment and during travel, and facilitates more frequent and/or prolonged dialysis.
- WAK and PAK devices are close to clinical application.
- A bioartificial kidney (BAK) provides an extension to conventional dialysis systems and artificial kidneys, by incorporating elements of living cellular and tissue function, in an attempt to better mimic the function of normal kidneys.
- Development of an autonomous, dialysate-free BAK may enable realization of an implantable device.

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Declaration of interest

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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