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Perspective

The Future for End-Stage Kidney Disease Treatment: Implantable Bioartificial Kidney Challenge

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Abstract: Despite limited organ availability and post-transplant complications, kidney transplantation remains the optimal treatment for End-Stage Kidney Disease (ESKD). However, innovative dialysis technologies such as portable, wearable, and implantable bioartificial kidney systems are being developed with the aim of addressing these issues and improving patient care. An ideal implantable device could combine bioreactors and blood ultrafiltration to replicate key native cell functions for solute reabsorption, secretion, and endocrinologic activities. Today, the feasibility of an implantable bioreactor for renal cell therapy opens the challenge of developing a fully implantable bioartificial kidney based on silicon nanopore membranes to ensure immunological isolation, cell viability, and the possibility of maintaining a blood substrate for metabolic activities. Current technology is not sufficient to obtain an efficient artificial bioreactor to reach physiological blood purification, which requires a more complex system to produce an ultrafiltrate from the blood that can be processed by cells and eliminated as urine. The number of cells in the bioreactor, endocrine activity, immunological cell isolation, solute and fluid secretion/reabsorption, cell viability, blood and ultrafiltration flow control, and thrombogenicity are fundamental issues that require a new technology that today appears to be a challenge for the design of an implantable artificial kidney. This review aims to analyze the state of the art in this particular field of kidney replacement therapy to highlight the current limitations and possible future technology developments to create implanted and wearable organs capable of treating ESKD with artificial organs that can replicate all native kidneys functions.

Keywords: end-stage renal disease; chronic kidney disease; kidney transplant; implantable bioartificial kidney; bioreactor

Citation: Nalesso, F.; Garzotto, F.; Cattarin, L.; Bettin, E.; Cacciapuoti, M.; Silvestre, C.; Stefanelli, L.F.; Furian, L.; Calò, L.A. The Future for End-Stage Kidney Disease Treatment: Implantable Bioartificial Kidney Challenge. *Appl. Sci.* **2024**, *14*, 491. https://doi.org/10.3390/app14020491

Academic Editor: Zhonghua Sun

Received: 30 November 2023
Revised: 3 January 2024
Accepted: 4 January 2024
Published: 5 January 2024

1. Introduction

End-Stage Kidney Disease (ESKD) represents the final, irreversible stage of chronic kidney disease, where the kidneys lose their ability to sustain the essential life-supporting functions due to significant and permanent damage. At this stage, kidney replacement therapies become essential for survival. The primary modalities of treatment include dialysis and kidney transplantation. Dialysis, which can be performed as either hemodialysis or peritoneal dialysis, involves mechanically removing waste products and excess fluid from the blood when the kidneys can no longer perform these tasks. Hemodialysis is typically performed in a clinic setting several times a week (usually three times per week), while peritoneal dialysis can be performed at home but requires daily treatment. Kidney transplantation, on the other hand, involves the surgical replacement of the kidney function

with a healthy kidney from a donor, living or deceased. Transplantation generally offers better quality of life and survival rates compared to dialysis but requires immunosuppressive medications to prevent organ rejection. Each of these therapies has its indications, advantages, and limitations, and the choice of therapy is individualized based on patient-specific factors including the underlying cause of ESKD, patient's overall health, lifestyle considerations, and personal preferences. This article reviews the state of the art of existing technologies for replacing the kidney function through the use of wearable and implanted artificial organs by analyzing their current limitations and possible future developments.

1.1. The End-Stage Kidney Disease and the History of Kidney Replacement Therapy

The total number of patients affected by End-Stage Kidney Disease (ESKD) saved by the artificial kidney can hardly be estimated, but it is surely very high. The history of dialysis technology evolution has one of its milestones in 1943, as the first practical dialyzer composed of a 20 m long rotating cellophane tube wrapped around a 2 m horizontal drum serving as a semipermeable membrane was realized by a Dutch physician, Doctor Willem Kolff [1]. The major limitation of this device, without considering the large extracorporeal volume required, was inappropriate body fluid removal, which is one of the most important issues during fluid overload in renal dysfunction. In fact, in this system, gravitation generates a transmembrane pressure that was not adequate to effectively achieve ultrafiltration as required by the patient's clinical status. Therefore, conditions characterized by fluid overloads, such as pulmonary edema or hypertension, could not be effectively treated by this device.

The opening success of this prototype was followed by the implementation of a modified dialyzer that was enabled to bear higher transmembrane pressure to ensure fluid removal [2]. Subsequent development of precise ultrafiltration control systems using scales and flow control have made fluid removal precise and safe making the fluid balance control an achievable and customizable clinical goal for each individual clinical setting. As the very first chronic dialysis facility was founded in Seattle in 1960, renal failure was no longer a fatal disease.

1.2. Current Extracorporeal Purification between Limitations and New Perspectives

Current hemodialysis techniques include hollow-fibered dialyzers that replaced the original giant rotating drum kidney and represent today essential therapeutical options for patients admitted to hospitals with acute kidney injury (AKI) or ESKD. Although these devices have been shown to extend the lives of patients, the existing blood purification technology is still not perfect, being based only on processes of removing molecules from the patient's blood.

New technology is needed to overcome the shortcomings represented by the patient's quality of life, intra-hemodialysis issues, and the still unmatched replacement of kidney metabolic functions. Although the available blood depuration system has improved in terms of effectiveness, efficiency, and biocompatibility, the principles of blood purification have not changed from the first generation of artificial kidneys. From this point of view, the main targets of dialyzers are solute clearance and fluid removal from the patient without providing molecule reabsorption, catabolism, and endocrine function which are active functions that can be performed by a more complex system than the dialysis filter. Bioengineering has developed a specific blood purification technology to achieve the removal of molecules retained during ESKD based on the specific dialyzer structure, performance, biocompatibility, and membrane material. Thus, research in this area is directed toward finding devices that are increasingly efficient in removing target molecules but without finding viable solutions in the area of reabsorption and secretion of specific molecules. Artificial kidneys and semipermeable membranes for blood purification are still a current matter of research. Due precisely to their future characteristic of being bioartificial, artificial kidneys could significantly implement extracorporeal purification by introducing the activities of secretion, reabsorption, and metabolic activity. The advances in synthetic

membranes, nanotechnology, and experience in dialysis have contributed to the potential of forthcoming dialyzer development; in fact, it took decades to develop the system of blood purification currently in use. Nowadays, such development allowed the move from regular dialysis for ESKD to Continuous Kidney Replacement Therapy (CKRT) in the Intensive Care Unit (ICU). The ability to have advanced and safe software and hardware to perform CKRT allows us replacement of renal function in a continuous way especially in highly critical and unstable patients that require continuous adjustment of renal metabolic compensation to their clinical needs. Despite these technological implementations, a lot of work is still to be conducted in order to improve the three major drawbacks of current hemodialysis techniques: patients' quality of life, technical problems that may occur during dialysis treatment, and the impossibility of replacing the kidney's metabolic functions [3].

The most important aspect that should lead the development of the new generation of artificial organs is that natural kidneys are not mere organs of filtration. As a matter of fact, they are also in charge of several metabolic functions, such as the synthesis of 1,25-dihydroxyvitamin D (1,25$(OH)_2$ D) [4], ammonia genesis [5,6], glutathione metabolism [7], erythropoietin production [8], and immunoregulatory support [9]. Thus, to truly fulfill every kidney function, the renal metabolic role is to be taken into consideration. In fact, modern designs of artificial kidneys put much emphasis on the efficiency of dialysis and fluid removal but not on its metabolic functions. From a clinical point of view, this lack of metabolic activity requires the use of specific drugs that must be administered to the patient according to a biochemical feedback that has to be regularly checked with blood tests. Therapeutic adjustments are therefore subject to a constant delay due to the inability to have continuous online feedback as is the case with the metabolic activities of the natural kidney. Typical examples are changes in the dose and frequency of erythropietin administration to maintain a constant hemoglobin in the patient, or the administration of vitamin D analogs to maintain proper bone metabolism. At present, the most effective approach to replacing organ function is the utilization of transplanted organs. Despite the limited organ availability and possible post-transplant complications, kidney transplantation remains the optimal treatment for ESKD. On the other hand, dialysis—both extracorporeal and peritoneal—is only life-sustaining and provides limited removal of uremic toxins. Despite the advances in technology, hemodialysis (HD) is still expensive, burdened by higher mortality, vascular access complications, and lesser quality of life and patient satisfaction compared with peritoneal dialysis, which, however, presents lower efficacy and a high risk of infections, which are the primary reason for transfer to HD [10]. Home hemodialysis (HHD) is believed to be more physiological and better tolerated by patients than in-center hemodialysis. Moreover, it has a number of advantages, including improved survival and quality of life (QOL), flexibility, and potential for employment compared to in-center hemodialysis [11–14]. Technological research has moved towards the improvement and miniaturization of home hemodialysis services in order to overcome the constraints of standard HD with the development of new purification devices, such as novel dialyzers that mimic active processes of ultrafiltration and secretion in the native kidneys [15], membranes, wearable technology and sorbents for regenerating dialysate. These advances represent the first step towards the development of implanted devices capable of fully replacing natural renal function.

The miniaturization of hemodialysis machines requires the development of advanced technologies that involve a multidisciplinary effort, including multiple clinical and technical elements such as vascular access, blood flow in the circuit, purification techniques, and catabolic and synthetic activity. Considering that at least 120 L of dialysate is required in a hemodialysis treatment, the regeneration of the waste fluid is necessary in order to allow the system downscaling into a portable device. The aim is to provide the elimination of substances through chemical breakdown and ion exchange [16,17] or adsorptions to maintain electrolyte concentration within the normal range. Commonly, prolonged treatments, especially CKRT, can clinically result in excessive removals of ions that require their external supplementation as is the case for phosphate and potassium. This is reflected in an overload

of work for nurses and a need for customization of treatments in terms of prescription, type of fluids used, and prescribed depurative dose. In a wearable/implantable device, this issue should be solved by intrinsic solutions in the device used minimizing external interventions by the physician, nurse, and patient. Specific devices can have an important role in this field not only to remove substances from dialysate, but also to exchange ions. The sorbent most commonly considered for this purpose is activated carbon. Historically, activated carbon was used in a home dialysis system that recirculated a 6 L batch of dialysate. Currently, the processing of spent dialysate by activated carbon (AC) is being considered to reduce the dialysate requirement for both hemodialysis and peritoneal dialysis. However, there is remarkably little research into the ability of activated carbon to remove different uremic solutes [18], in particular urea, that, in contrast to other organic waste compounds, binds poorly to sorbents (affinity for AC∼0.1 mmol/g). In addition, its amount is consistent, ranging from 240 to 470 mmol/day, making it the primary nitrogenous waste product of the metabolism [19]. The need to tailor the purifying dose to the individual metabolic needs of the patient plays an important role and represents a challenge for new implantable devices. According to the technology available for wearable miniaturized devices, urea removal can be obtained by the use of urease-catalyzed hydrolysis into bicarbonate and ammonium, which is more toxic than urea. In this case, zirconium phosphate may be used to remove ammonium by the dialysate; the bicarbonate released by hydrolysis, instead, reacts with protons to generate water and carbon dioxide, effectively removed from the dialysate closed-loop system [20]. Urea removal at the rate of 16 mmol/h is also possible, taking advantage of its electrochemical decomposition into N_2 and CO_2, which can be outgassed from the dialysate by using a device with reusable graphite electrodes [21]. Cartridge uptake could be another solution to urea removal in an effective, simple, and safe way. Sorbents can remove urea from dialysate either by forming covalent or coordination bonds (chemisorption) or by non-covalent bonds (van der Waals forces, dipole interactions, and hydrogen bonds, i.e., physisorption). However, in physisorption, even if the process is faster, the resulting bonds are weaker with sorbent-bound urea in equilibrium with urea dissolved in the dialysate, resulting in a lower removal efficiency [22]. Recent developments have shown the potential of sorbents for the effective removal of urea from the dialysate, among which are silicon dioxides (silica) and zeolites; however, aluminum leaching from zeolites is a potential hazard for the patient. All these solutions, although very interesting and fascinating from a technical point of view, still pose a whole series of limitations that make their use strictly experimental in prototypes that are unlikely to evolve into implanted and indomitable purification systems in the near future, although the wearable artificial kidney (WAK) could be a very promising way to provide a practical solution to the needs of patients. However, at present, only a few technical proposals have tried and are trying to achieve a realization of the WAK system to be used in clinical practice [15]. Gura et al. demonstrated that treatment with the wearable artificial kidney was well tolerated, resulting in the maintenance of electrolyte and fluid homeostasis with effective uremic solute clearance. However, of the seven enrolled subjects, only five completed the planned 24 h treatment study. In fact, the trial was stopped because of device-related technical problems, such as excessive carbon dioxide bubbles in the dialysate circuit [16]. One of the most critical elements for extracorporeal purification in wearable devices is the ability to regenerate dialysate for long periods. Sorbent-based dialysate regeneration system has been effectively applied to the treatment of acute and chronic kidney failure patients for many years, and now it seems to have great potential in this research field. However, there are issues associated with the use of sorbents and resins to maintain the pH and electrolytic composition of the dialysate in the range required by the patient's clinical condition. In their preliminary report, Gura et al. [16] demonstrated that patients tolerated this treatment very well and were allowed eating and drinking, as about 1 L of water was removed by ultrafiltration, with no significant change in blood pressure. Moreover, they demonstrated patient feedback in terms of a lack of interdialytic symptoms and a minimal to zero recovery time post treatment; patients were equally positive in their perception of the therapeutic

potential of this device in terms of facilitating treatment flexibility, freedom, and improved lifestyle. The clinical subjective impact of such technology appears to be positive, with patients' perception that the system is safe and easy to use in daily life. These findings confirm that by redesigning to address the identified technical issues, a wearable artificial kidney can be successfully created as an innovative and feasible alternative to traditional dialysis technology. An ideal implantable bioartificial kidney could overcome the problem of dialysate regeneration by mimicking the full renal function. This could be achieved by combining bioreactors and blood ultrafiltration to replicate key native cell functions for solute reabsorption, secretion, and endocrinologic activities (1,25-OH-vitamin D and erythropoietin production). In order to mimic the complex renal functions and to achieve fluid balance and waste removal [23] by filtration and secretion, the implantable bioreactor needs to be combined with an ultrafiltration system. This ensures the reabsorption of useful molecules such as bicarbonate, amino acids, glucose, and phosphate.

In the context of nephrology, and specifically in the field of extracorporeal blood purification, a bioreactor can be defined as a specialized device designed to support the growth, maintenance, and function of renal cells or tissues in a controlled environment to mimic the physiological kidney function to provide a platform for blood purification to improve dialysis technology development with metabolic and molecule reabsorption and secretion activities.

In a nutshell, the future of artificial kidneys aims at miniaturization and implantability, better biocompatibility, and metabolic function combining all available technology. It is undoubted that membranes are the fulcrum of extracorporeal treatment, and technological advances in membrane design, chemical composition, and sterilization methods lead to enhanced performance with the reduction of dialysis "unphysiology". Modifications of the composition of HD membranes have improved their biocompatibility and improved patient quality of life. Specifically, membranes composed of polymeric or inorganic material appear to be more efficient for the removal of uremic toxins compared to synthetic membranes. However, membranes utilized for hemodialysis are efficient in the removal of small water-soluble solutes and toxins, but their efficiency decreases proportionally for middle to large molecules and toxins. Protein-bound uremic toxins are also hard to remove. Ideally, membranes have to mimic glomerular filtration [24] with molecular weight cut-offs up to ~66 kDa [25]. The prolonged use of these membranes, while mimicking the continuous kidney filtration, leads to issues such as biocompatibility and filter patency, becoming a further challenge for the development of implantable devices. In order to implement biological functions and purification efficacy, the novel membranes could be combined with bioartificial kidneys, where artificial membranes are combined with kidney cells in bioreactors. To overcome the shortcomings of current devices for artificial kidneys, studies and trials of silicon nanopore membranes, tissue engineering for renal cell bioreactors, and dialysate regeneration are under development. With future advancements, wearable or implantable artificial kidneys will be soon achievable [26]. The feasibility of an implantable bioreactor for renal cell therapy was demonstrated by Kim et al. [27], opening the challenge to the development of a completely implantable bio-artificial kidney (iBAK). Such a device is based on silicon nanopore membranes that ensure immunological isolation, cell viability, and the possibility of maintaining a blood substrate for metabolic activities.

Research in the field of membranes is developing new materials to overcome the limitation of blood purification in wearable and implanted devices due to the actual structural limitation of classical dialyzers. The new synthetic dialysis membranes are composed of hydrophobic polymers blended with Polyvinylpyrrolidone (PVP) or other additives to improve biocompatibility, although the long-term use and sterilization process can elute them, reducing compatibility [28,29]. To resolve this problem, polyvinylidene fluoride membranes are coated with polyvinyl alcohol and chitosan. This improves biocompatibility [30] and can determine white cells, complement activation, and filter clotting. The issue of filter clotting can be reduced by using membranes with grafted argatroban onto the surface of polysulfone membrane [31], achieving a good anti-thrombogenic effect. Despite

all these implementations, the potential miniaturization of this new type of membrane is limited [32] due to permeability limitations caused by fiber geometry and hydraulic resistance, which requires bulky devices. Another membrane limitation is its relatively broad pore size distribution that limits filtration selectivity, which is now overcome by silicon-based nanoporous membranes (SNMs) presenting uniform nanopores with a deviation between pore sizes of less than 1% [32–34]. In order to enhance permeability due to their low porosity, these SNMs have been fabricated with arrays of nanoslits (10 nm wide and 4.5 μm long) [34], presenting uniform nanopores suitable for hemodialysis and hemofiltration. Their limitation in clinical use concerns the poor silicon hemocompatibility, which requires a hydrophilic coating with polyethylene glycol (PEG) to prevent activation of macrophages, innate immunity dysregulation, and inflammation. This technological solution is not definitive [34], as in an implantable artificial kidney, the PEG can quickly degrade, so much longer-lasting alternatives are needed. The combination of a hemocompatibility inner porous layer based on polyethersulfone/polyvinylpyrrolidone (PES/PVP) and an outer layer of activated carbon dispersed within a matrix of PES/PVP in contact with the dialysate can determine low cell adhesion with improved hemocompatibility, associated with enhanced toxin removal by diffusion/convection and inner membrane layer adsorption by activated carbon particles, which leads to a high toxin concentration gradient across the membrane, thus stimulating the further dissociation of protein-bound toxins from plasmatic proteins. This process can enable the application of lower amounts of dialysate than conventional hemodialysis membranes. Additionally, this membrane structure can protect the patient from bacterial pyrogen contamination from the dialysate [35]. It seems that the development of such membranes introduces important advantages for implantable systems, where a low quantity of dialysate is required for prolonged application. The permanence of such implanted devices for a prolonged period could result in the deterioration of dialysate characteristics, including bacterial contamination, and any form of patient protection could be helpful. To mimic the glomerular filtration, the characteristics of current membranes had to be implemented in the WAK, and the system supplied with a closed-loop dialysate regeneration system. Otherwise, to mimic the tubular reabsorption of water, ions, glucose, and amino acids from the filtrate, it is necessary to imply a specific technology based on ion exchange resin combination, ion exchange membranes, and an externally applied voltage to achieve selective ion reabsorption.

1.3. Bioreactors for Artificial Kidneys

Bioreactors may in the future provide metabolic support to the filtration and absorption activities determined by current dialysis filters. Combined plasmatic water filtration systems and ultrafiltrate and blood reprocessing devices are the basis of more complex devices directed at blood purification (Figure 1). The use of cultured proximal cells on artificial membranes in the implantable Bioartificial Kidney (iBAK) aims at mimicking proximal tubule function. However, cell source availability, distribution, storage, and the following reconstruction represent a challenge. The chance to design an experimental bioartificial renal epithelial cell system in niobium-coated carbon disks covered with renal epithelial cells from adult progenitor kidney cells discloses the possibility of cryopreserve and cryostorage this device so that it can be carried and thawed at the end-use location [36]. The combination of immortalized proximal tubule epithelial cells on functionalized hollow fibers with conventional hemodialysis filters makes this technology able to mimic glomerular filtration, tubular secretion, and reabsorption, thus allowing the most "physiologic" and complete replacement of kidney functions [37,38]. The availability of such technology has enabled the realization of an animal iBAK prototype consisting of an SNM hemofilter with sub-10 nm wide slit pores in series with a porcine renal cell (LL-CPK1) bioreactor unit cultured on as SNM.

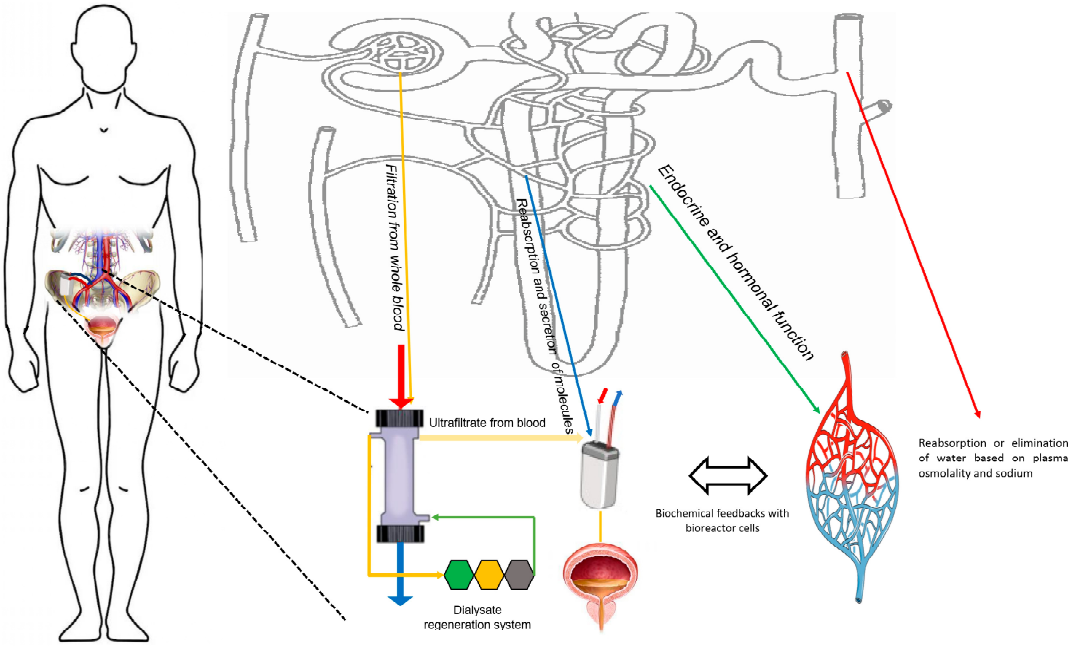

Figure 1. iBAK and nephron, integration of nephron activities into a modular and complex device. In red, blood entering the device; in blue, blood leaving the device. In yellow, the dialysate and ultrafiltrate processed by the filter and bioreactor. The functions of filtration, reabsorption from the ultrafiltrate, secretion into the ultrafiltrate, regeneration of the dialysate, production of hormones, and modulation of water reabsorption/excretion are handled by different devices combined with the bioreactor in a more complex device.

Currently, the only device with relevant clinical results for the future development of an iBAK appears to be the WAK designed by Gura [16,39]. The WAK has been tested only in three small clinical trials so far in two different hemodialysis duration regimens, shorter (up to eight hours) and longer (24 h), respectively. Ultrafiltration and clearances of urea, creatinine, and phosphorus have been revealed to be effective. The major criticalities of this system concern the formation of bubbles, coagulation of the filter and lines, and the need for continuous treatment in order to achieve an effective and clinically relevant middle molecule clearance in a diffusive modality. The combination of diffusion and convection can increase purification efficiency, but in wearable and implanted devices, it is limited by the low volumes of dialysate and the inability to regenerate ultrafiltrate. This problem may be partially overcome by the implementation of a "push–pull" pump, a process that produces an alternating transmembrane pressure with a small volume of dialysate back and forth across the dialyzer, thus generating a convective force that improves middle molecule clearance. The integration of this system with microvalves and standard silicon and microelectronics technology would allow the opening and closing of fluidic channels and fluid pumping, rendering it available for wearable devices [40].

2. Future Perspective beyond Current Technical Limitations

It is evident that the current technology was developed to overcome individual technical problems [41] but did not lead to real integrations in the artificial kidney development, as modern devices cannot mimic all kidney functions. The experimental results obtained so far have opened up the future for the design of prototypes to be used in clinical trials. Individually, these experimental achievements are not enough to obtain an efficient artificial bioreactor to reach physiological blood purification. To reach this objective, a new type of implantable iBAK is necessary. The iBAK may be inserted into a more complex system able to provide a ultrafiltrate from the blood to be processed by cells and eliminated as "artificial urine" through a stoma or bladder. At the same time, the contact between blood and the bioreactor should be able to provide nutritional substrates to renal cells and guarantee their

endocrine activity (Figure 1). While the use of silicon nanopore membranes looks very promising for the realization of a future iBAK [27], some technical aspects appear to limit its use. The number of renal cells in the bioreactor (1.2×10^7 cells vs. 5×10^9 proximal tubular cells in a human kidney) [42], compared to a physiological nephron mass, is too low to guarantee physiological solute secretion, reabsorption, and hormone production. Immunological isolation may no longer be effective as the number of cells increases, exposing them to damage and death. Cell viability could be limited in time, clearly opening the problem of a faster frequency of cell replacement in the bioreactor, which is not ideal for an implantable device whose functioning should last for several months. Another key point is the control of the blood flow and the regulation of ultrafiltration for fluid removal. Indeed, the blood flow in the iBAK should be based on the arteriovenous gradient with safe flow-pressure feedback to ensure continuous bioreactor perfusion, maintaining stable fluid ultrafiltration for continuous artificial urine production. Such a control mechanism also requires an engineering challenge in terms of fluid removal, which should rely on patient hematocrit and blood protein levels to maintain the patient euvolemic state. In the event of patient hypovolemia, fluid reabsorption from the artificial urine is a major engineering challenge. This is due to its physical and biochemical complexity in terms of simultaneous reabsorption of sodium and water in relation to plasma osmolality [43]. This issue requires the use of advanced technology that allows the regulation of plasma osmolarity with complex feedback, including algorithms for the management of ultrafiltration [44], blood flow, and fluid reabsorption or elimination. The synergy of these ultrafiltration mechanisms becomes essential in anuric patients in whom a correct fluid balance is essential to avoid hypervolemia and its complications, such as acute pulmonary edema. On the other hand, the ability to concentrate on the device becomes essential in patients with preserved diuresis in order to avoid states of dehydration. The lack of bioreactor ability to regenerate bicarbonates and eliminate hydrogen ions could have repercussions on the maintenance of the acid–base balance. Likewise, the lack of feedback for aldosterone could indicate a deficiency in potassium secretion and sodium reabsorption, while the lack of ADH target cells could lead to clinically significant variations in plasma osmolality. All such activities cannot be recreated through bioreactors containing a single cell line, requiring different cell types for these specific functions. Concentrating multiple cell lines in a single bioreactor is currently unthinkable. This is due to the different interactions between blood and ultrafiltrate depending on the specific functions that must be performed. An additional problem comes from the thrombogenicity of the device, which may be overcome by using extremely biocompatible materials to minimize the thrombogenic effect of blood contact. Furthermore, in the quest for miniaturization for implantability, the geometry of the ultrafiltration device must provide an adequate and uniform distribution of the blood flow for an ideal ultrafiltration profile [45]. This configuration allows maximization of the blood flow, obtaining the best ultrafiltration in relation to the utmost miniaturized filtering surface to guarantee its implantability. Wearable ultrafiltration devices (WUF) and WAK have already been tested in humans [46] with encouraging clinical results. However, their technical limitations have discouraged their further development; such barriers concern the vascular access provided by a Central Venous Catheter (CVC), the need for systemic anticoagulation, the weight of the device (1.1 Kg), its wearable and non-implantable nature, and the low battery life [47]. All the above restraints may be solved with innovations in the field of artificial kidneys through the utilization of new disciplines such as nanotechnology, materials physics, materials engineering, miniaturization, and microfluidics [48], leading to a new era of dialysis in which the new challenge is the development of the iBAK that could eventually save millions of lives [49].

The technological process of transition from in-center to home hemodialysis requires the miniaturization of devices and the introduction of technological innovations that enable their progressive use toward wearability. Current technology is limited, as hemodialysis therapy removes a limited range of uremic toxin discontinuously and requires large volumes of dialysate, thus limiting the portability and patient quality of life and autonomy.

The first issue to be addressed concerns the reduced volume of dialysate needed and its regeneration in wearable and implanted devices. The use of different types of sorbents for this purpose has an impact on the ecological footprint of sorbent production and recycling. The reduced removal of uremic toxins resulting from the reduced volume of dialysate in wearable/implanted devices is compensated for by the use of polymeric or inorganic materials in novel dialysis membranes. Such innovative membranes can improve the removal of a broad range of molecules by filtration and adsorption, thus ensuring high efficiency and low levels of membrane fouling compared with currently available membranes for classical hemodialysis. The function of seemingly simplistic uremic toxin removal has to be coupled with biological functions to replace every function of the kidney, such as the production of erythropoietin and vitamin D. This requires the combination of artificial kidneys with bioreactors able to ensure not only the production of hormones but also the catabolism of drugs and the reabsorption of useful molecules from the ultrafiltrate processed in the system (Figure 1). In this way, the physical diffusive and convective processes can be exploited to the fullest to achieve a purification target that maintains the metabolic balance in the patient without leading to the loss of useful molecules in the purification process. In this scenario, the synthetic metabolic demand and the reabsorption process have to be ensured by the use of kidney cells capable of surviving and maintaining metabolic functions for long periods while reducing maintenance interventions on the device. The biggest problem concerns the kidney cell source, their culture facilities attached to dialysis centers, and finally the large-scale low cost. The complexity of such a system raises a number of issues concerning manufacturing, feasibility, and logistics. A complex implantable artificial kidney would have much lower blood flow resistance than an extracorporeal device. Using natural blood pressure as a driving force would avoid the need for an artificial blood pump and reduce the energy supply requirements. This configuration can be achieved by the connection of iliac vessels, but anastomosis, blood compatibility, and surface thrombogenicity can represent critical issues of implanted devices. To overcome these problems, heparin-coated surfaces can be used even though their stability, in the long run, is not optimal, and alternative solutions with polyethylene glycol have limited effects. Certainly, vascular access becomes a key topic for implanted devices that have to be maintained in place for months/years. These vascular accesses have to ensure easy and rapid replacement of attached devices, adequate blood flow, and reduced risk of clotting even during relative hypotension or hypovolemia due to concomitant acute and chronic diseases. A promising solution is the coating of silicon membranes with sulfobetaines [50]. The implanted device requires a balance between dimension and membrane surface to guarantee the filtration and the possibility of increasing the number of renal cells in the bioreactor in order to provide physiological solute secretion, reabsorption, and hormone production. If this device were to be implanted with invasive surgery, it would require a product safety level and mean time between failure and lifetime like that of a Ventricular Assistance Device in order to make the patient not dependent on continuous maintenance interventions or surgery.

Finally, the complexity of renal physiology requires the development of a composite iBAK, which should be the result of the collaboration of multiple disciplines for the development of a technology to artificially reproduce all kidney functions. The possibility of introducing complex iBAKs could allow the development of distinct modular devices the replacement of every single renal function (ultrafiltration, hormone production, reabsorption, molecule secretion, metabolism, fluid balance, etc.). The integration and progressive miniaturization [51] of these modules will allow the development of devices the ability to replace renal functions more effectively than current therapeutic options, which focus on solving individual problems rather than integrating functions. The chance to adopt a modular device composed of individual units will also empower better maintenance management of the device by making it possible to replace or repair a single part instead of the entire device. The real challenge of the future to guarantee the replacement of renal function through an artificial organ, therefore, lies in the development of a complex iBAK or

artificial transplantable kidneys from organoids [52,53]. Table 1 shows the available blood purification devices with their limitations and possible future uses in iBAK, while Table 2 shows the limitations of blood purification devices compared to natural kidney functions.

Table 1. Available blood purification devices with their limitations and possible future use in iBAK.

Device	Type of Device	Mechanism of Purification	Limits	Future Developments	Integration in IBAK Implantable
Battery	Source of electric power	device pumps support	time-limited duration	long-lasting durability	Yes
Pumps	Peristaltic pumps or other pumps	maintaining the flow of fluids involved in purification	energy consumption, range of fluid flows achievable	improved energy, mechanical, and miniaturization efficiency	Yes
Bags of fluids	Fluid for hemodiafiltration	diffusion and/or convection	limited usable volume in implantable devices	on-line fluid regeneration systems	No, required closed dialysate circuits or closed ultrafiltration/reinfusion circuits after fluid regeneration
Filter for HD	Filter for diffusion	diffusion of molecules	range of molecules removed (molecular weight below albumin)	greater selectivity for molecules with possible adsorption on the membrane surface	Yes, with limitations for the spectrum of diffusible molecules and the generation of fresh dialysate
Filter for HF	Filter for ultrafiltration	convection of molecules	range of molecules removed (molecular weight below albumin)	greater selectivity for molecules with possible adsorption on the membrane surface	Yes, with limitations for the generation of infusion fluids
Filter for HDF	Filter for hemodiafiltration	diffusion and convection of molecules	range of molecules removed (molecular weight below albumin)	greater selectivity for molecules with possible adsorption on the membrane surface	Yes, with limitations for the generation of infusion and dialysate fluids
Cartridge for adsorption	Adsorption on blood	physisorption, chemisorption	hemocompatibility, saturation, selectivity	greater selectivity, haemocompatibility, and durability; combination of several cartridges	Yes, with limitations for device lifetime and selectivity
Bioreactor	Bioreactor with kidney cells	metabolic mechanism, endocrine function, possible reabsorption and processing of useful molecules from the ultrafiltrate	reduced number of usable cells, limited cell life, limited total device lifetime	immortal cell lines, longer overall life of the implanted device	Yes, with a limitation for device lifetime
Reinfusion of electrolytes	fluids	correction of electrolyte and acid-base disorders	limited usable volume in implantable devices	regeneration systems based on absorption and chemical reactions	Very difficult for high-volume requirements

HD: hemodialysis, HF: hemofiltration, HDF: hemodiafiltration.

Table 2. Available blood purification devices have their limitations compared to natural kidney functions.

Device	Filtration Function of Glomerulus	Molecules Reabsorption by Tubular Nephron Cells	Molecule Secretion by Tubular Nephron Cells	Endocrine Function	Water Reabsorption by Distal Nephron	Uremic Toxins Purification
Filter for HD	NO	NO	NO	NO	NO	narrow spectrum
Filter for HF	NO	NO	NO	NO	NO	broadened spectrum
Filter for HDF	NO	NO	NO	NO	NO	broadened spectrum

Table 2. *Cont.*

Device	Filtration Function of Glomerulus	Molecules Reabsorption by Tubular Nephron Cells	Molecule Secretion by Tubular Nephron Cells	Endocrine Function	Water Reabsorption by Distal Nephron	Uremic Toxins Purification
Cartridge for adsorption	NO	NO	NO	NO	NO	broadened spectrum
Bioreactor		YES	YES	YES	NO	NO
Bioreactor combined with filtration system	YES	YES	YES	YES	NO	broadened spectrum

3. Summary

The kidney comprises numerous complex functions that, until now, have been replaced by extracorporeal purification techniques aimed at removing a narrow spectrum of molecules through diffusion and convection. Metabolic (reabsorption and secretion of specific molecules) and endocrine functions have not yet been specifically and completely reproduced by the purification techniques available for clinical use. The feasibility of implantable bioreactors for renal cell therapy opens the challenge of developing a completely implantable bio-artificial kidney (iBAK) based on silicon nanopore membranes that ensure immunological isolation, cell viability, and the possibility of maintaining a blood substrate for metabolic activities. The development of specific technologies for keeping renal tubular cells alive for long periods in complex devices is of particular interest, as it forms the basis for achieving the metabolic and catabolic functions of artificial kidneys. The possibility of having separate modules for the management of individual kidney functions (filtration, molecules diffusion, reabsorption of water and solutes, endocrine and catabolic activity of drugs, and immunomodulation) will make it possible in the future to build complex, implantable devices, the lifetime of which will allow patient treatment without the need for continuous invasive maintenance. The challenge for the future is to miniaturize the individual modules and integrate them into complex devices that can be implanted in patients with ESKD while ensuring acceptable lifetime.

The complexity of iBAKs requires a multidisciplinary effort with the support of regulatory agencies such as the FDA, the EMA, and EU-notified bodies, as well as standards-issuing organizations, to promote innovation and expedite access to the new technology in this field.

Author Contributions: Conceptualization, F.N. and F.G.; methodology, F.N., F.G., L.C., E.B., M.C., L.F.S. and C.S.; validation, F.N., L.F. and L.A.C.; formal analysis, F.N., F.G. and L.F.; writing—original draft preparation, F.N., F.G., L.C., E.B., M.C., L.F.S. and C.S.; writing—review and editing F.N., F.G., L.F. and L.A.C.; supervision F.N. and L.A.C.; F.N. and F.G. contributed equally. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

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