Xenotransplantation, Wearable, and Implantable Bioartificial Kidney—What's upcoming for patients with kidney disease?

The Kidney Updates 2022

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Speakers Disclosure

Category	Disclosure Information
Current Employer	Penn State Health Hershey Medical Center
Research Funding – Pharma	TARGET BP I (Ablative Solutions) Membranous Nephropathy Trial--MAJESTY (Genentech/Roche) Ig-A Nephropathy Trial--Remegen
Speakers Bureau/Patents	Bayer

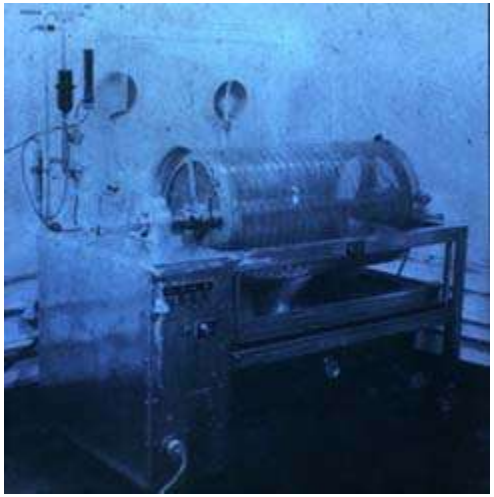
I will be discussing 'non-FDA approved' devices and reports in various stages of experimental and trial phases

Early days of Dialysis

The early development of hemodialysis

- 1861 The process of dialysis was first described by Thomas Graham from Glasgow
- 1913 Artificial kidney developed - John Abel (Baltimore) (never used on patient)
- 1924 First human dialysis - George Haas from Germany. 15 minutes treatment
- 1943 The first practical Rotating drum dialyzer - Kolff and Berk (Kampen)
- 1948 Kolff-Brigham machine. As used in the Korean war for acute renal failure
- 1965 Reports of home hemodialysis of four patients in Boston (Hampers et al) and two in Seattle (Curtis et al) and two patients in London

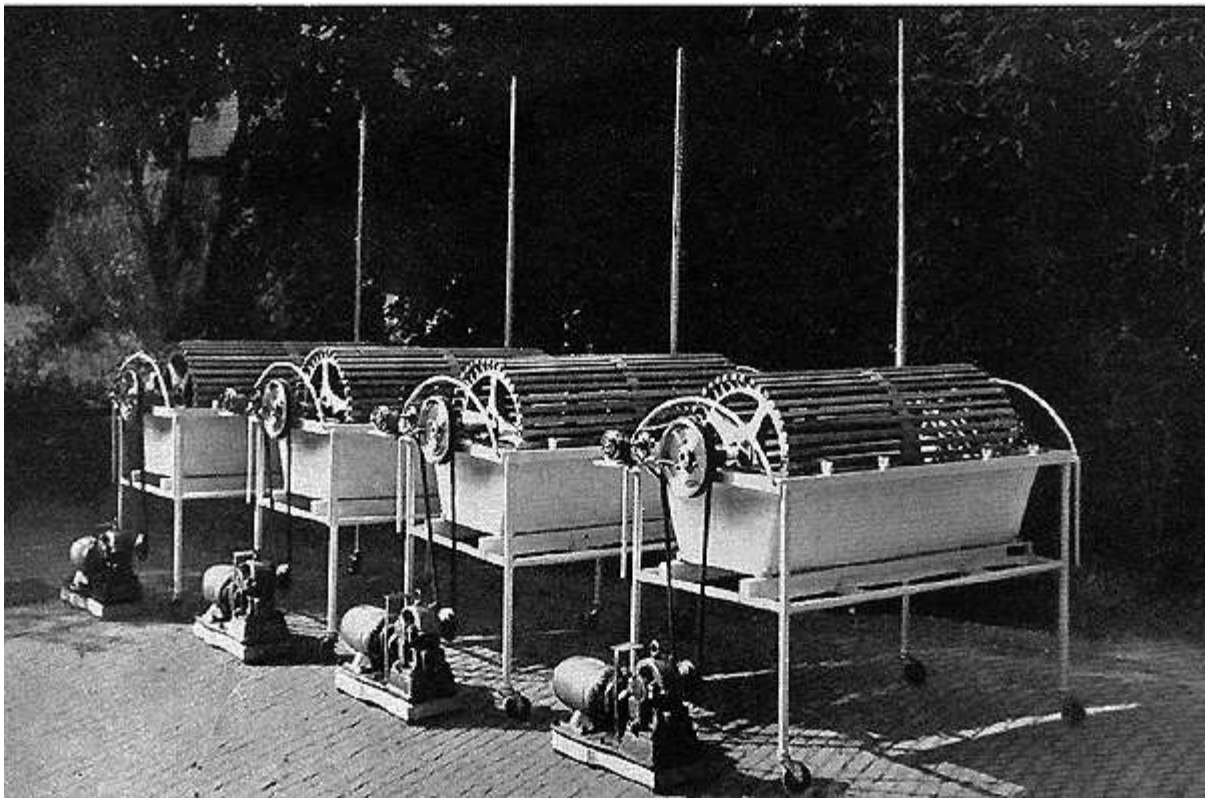
One of Kolff's first artificial kidneys (1946)



The Kolff-Brigham dialyser, 1948, a modified version of the original rotating drum kidney.

http://renux.dmed.ed.ac.uk/EdREN/Unitbits/historyweb/HDWorld.html

Figure 1. Rotating-drum artificial kidneys.
Four are shown ready to be shipped abroad. In 1946, one was sent to London; one to New York; one to Montreal; and the last one to Poland.

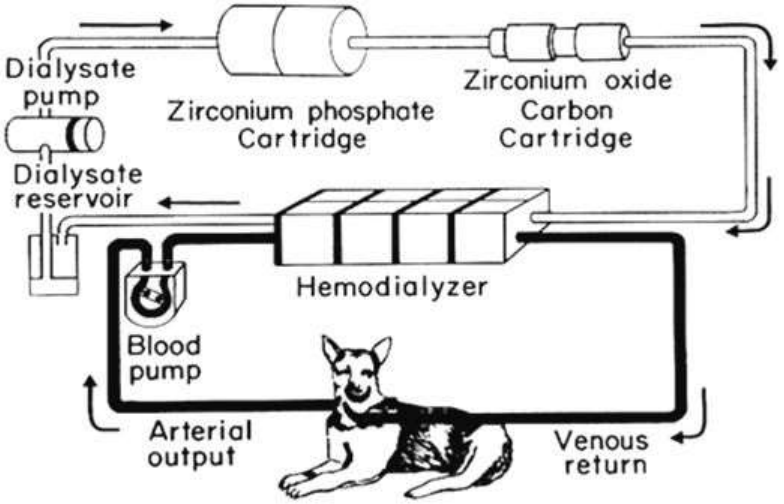


Nature Medicine 8, 1063 - 1065 (2002)
doi:10.1038/nm771

Early efforts for portable dialysis.

- **In 1969 Gordon and Maxwell introduced the concepts of portable dialysis devices with sorbent based low volume recirculating dialysate system.**

- **In 1970's Willem Kolff experimented with a wearable machine and reported its use**



Gordon A, Greenbaum MA, Marantz LB, McArthur MJ, Maxwell MH: A sorbent based low volume recirculating dialysate system. Trans Am Soc Artif Intern Organs 15:347-52, 1969

Dharnidharka SG, Kirkham R, Kolff WJ: Toward a wearable artificial kidney using ultrafiltrate as dialysate. Trans Amer Soc Artif Intern Organs 19:92-97, 1973

Dr. Willem J. Kolff (1911-2009) invented the first artificial kidney, built the first artificial heart, and developed a membrane oxygenator

'Dialysis in Wonderland' as described by the Legend:

- In 1970, we came up with a device to rehabilitate patients dependent for life on hemodialysis: the Wearable artificial kidney. The wearable unit consists of a combined blood and dialysate pump (1.2 kg), rechargeable batteries, tubing, dialyzer and a charcoal regeneration module with a **total weight of 3.5 kg.**
- Using the Wearable artificial kidney, we could send patients on what we called 'Dialysis in Wonderland' trips**. In 1 year, we made 28 such trips. Patients would raft down the Colorado River and dialyze themselves on shore, or they would drift down the Salmon River in Idaho and live on a houseboat on Lake Powell or go to the Bahamas or Hawaii, dialyzing in the mornings and perhaps water-skiing in the afternoons**.
- These 'Dialysis in Wonderland' trips were excellent programs to rehabilitate renal patients and show them that despite their kidney problems, they could still enjoy life.

Nature Medicine 8, 1063 - 1065 (2002)
doi:10.1038/nm771

Challenges to develop portable dialysis…

Challenges of Portable or Wearable mode of dialysis

- Size, weight and portability
- Infection and Clotting
- Long term access (blood or peritoneal)
- Efficacy and safety
- Energy efficient pumps and need for miniaturization and micro-fluids
- Better sorbents
- Biotechnology

What are sorbents?

Sorbents

- Used or spent dialysate passes through series of sorbents.
  - Urease layer to clear urea→ NH3 + CO2
  - Zirconium
  - Micro porous carbon
  - Gas permeable plastic de-aerating chamber for CO2 macro and micro bubbles
- Saturates over time and needs replacement and refreshment to correct electrolyte changes.

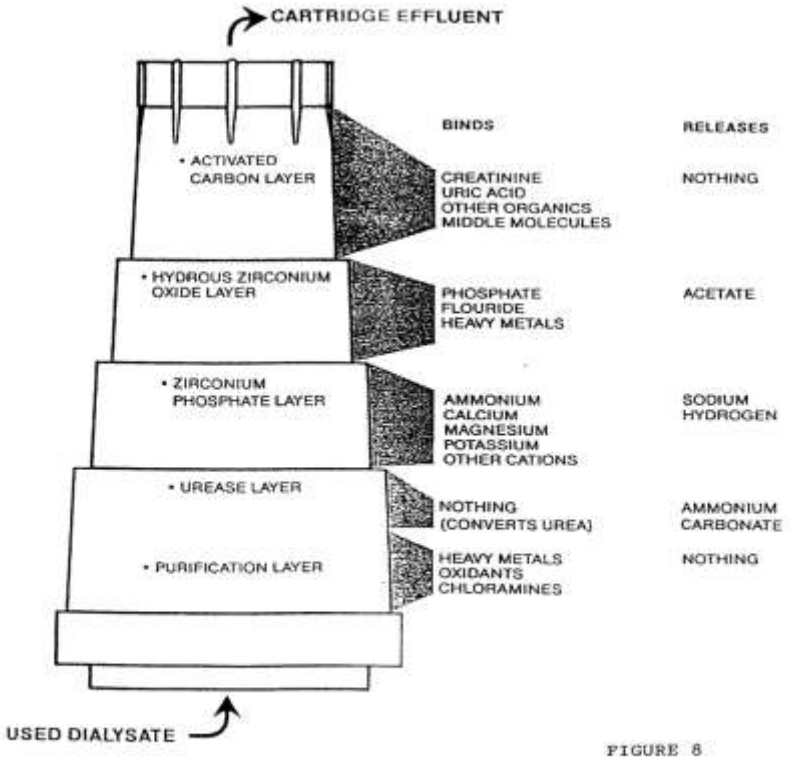
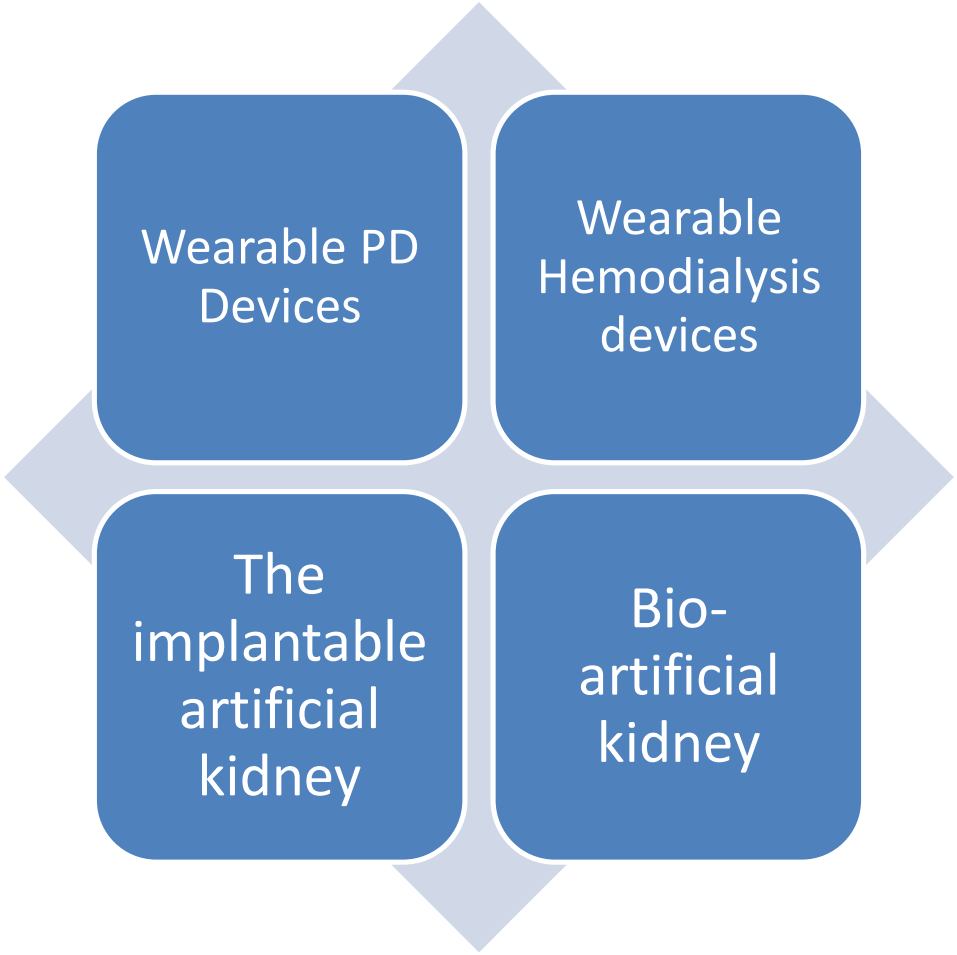


FIGURE 8

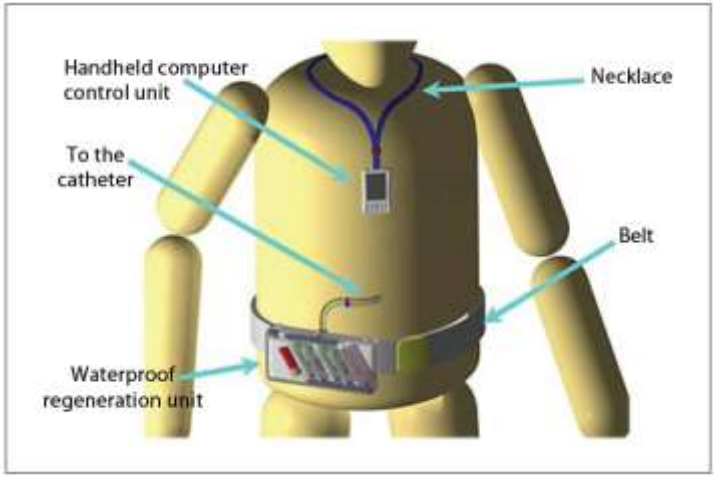
Some futuristic modalities….



Peritoneal dialysis (PD)-based wearable device

- ViWAK

(Vicenza wearable artificial kidney)

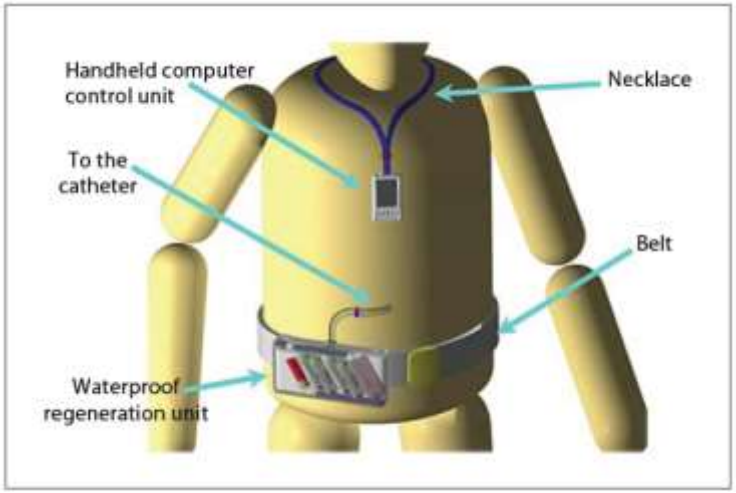


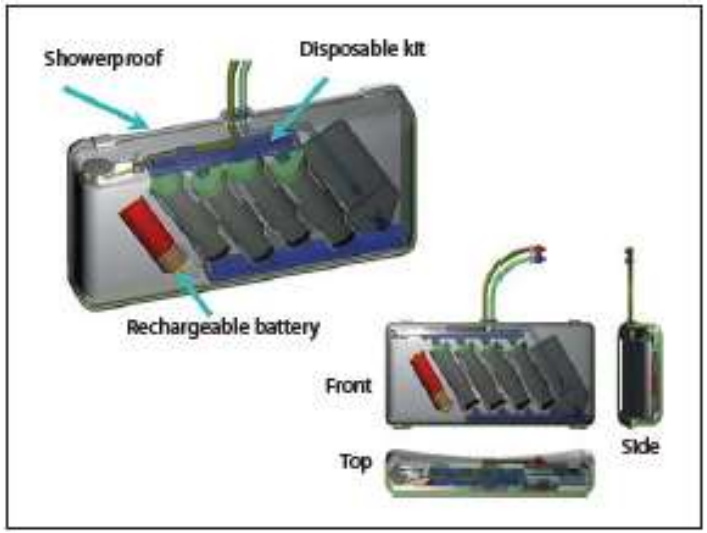
- AWAK

(Automated wearable artificial kidney)

ViWAK
(Vicenza wearable artificial kidney)

- A double lumen peritoneal catheter
- Dialysate outflow and inflow line
- Miniaturized rotary pump
- A circuit for dialysate regeneration featuring a waterproof container with 4 cartridges in parallel with a mixture of activated carbon and polystyrenic resins
- Filter for deaeration and microbiological safety
- Handheld computer as a remote control
- After an initial 2-h dwell with standard glucose-based dialysate, peritoneal dialysate is then continuously recycled by the passage of spent dialysate through a series of sorbents.
- Still experimental





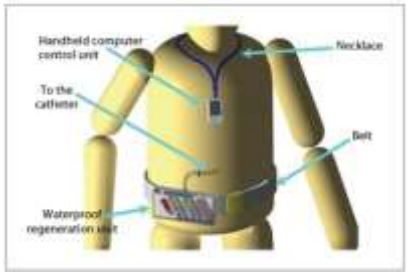
Claudio Ronco, Luciano Fecondini; The Vicenza Wearable Artificial Kidney for Peritoneal Dialysis (ViWAK PD) Blood Purif 2007;25:383–388

ViWAK
(Vicenza wearable artificial kidney)

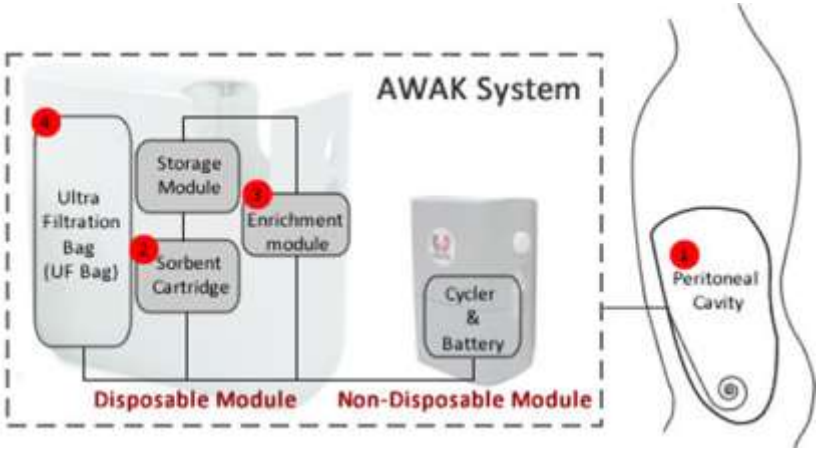
- The patient reduces the number of exchanges compared to CAPD and uses less fluid than in automated peritoneal dialysis (APD)

- No system to correct electrolyte changes or ultrafiltration control which can be achieved by overnight Icodextrin 7.5% exchange.

- Still needs a system to reduce fibrin delivery to the sorbent and a complex sorbent system to make sure a complete removal of small molecules including urea.

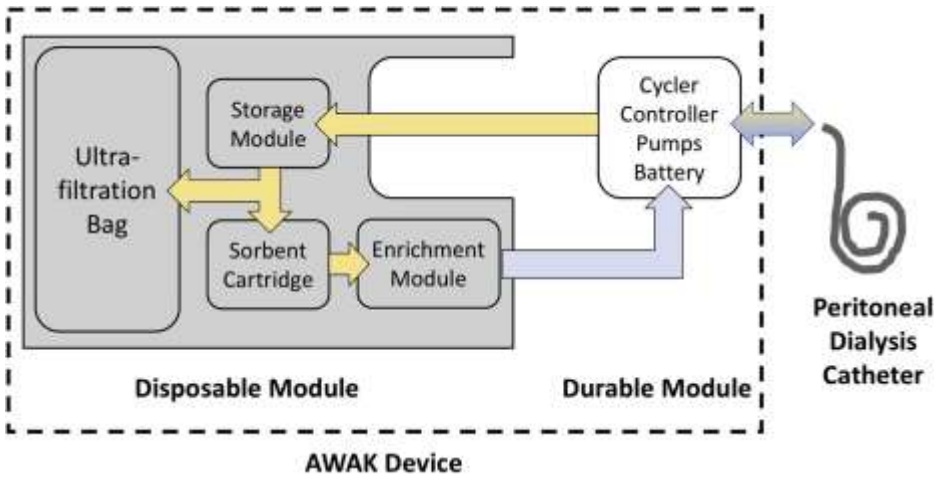


AWAK
(Automated wearable artificial kidney)



AWAK
(Automated wearable artificial kidney)

- PD based device for continued use with double catheter lumen access
- 1 to 1.5 L of dialysate (the reserve volume) is instilled into the peritoneal cavity
- Around 500 ml of fresh dialysate is recirculated in a tidal manner at 4 l/h using a battery-powered pump
- Any ultrafiltrate generated over an 8–10-h period drained into a separate bag attached to the module
- Battery life 18 hour



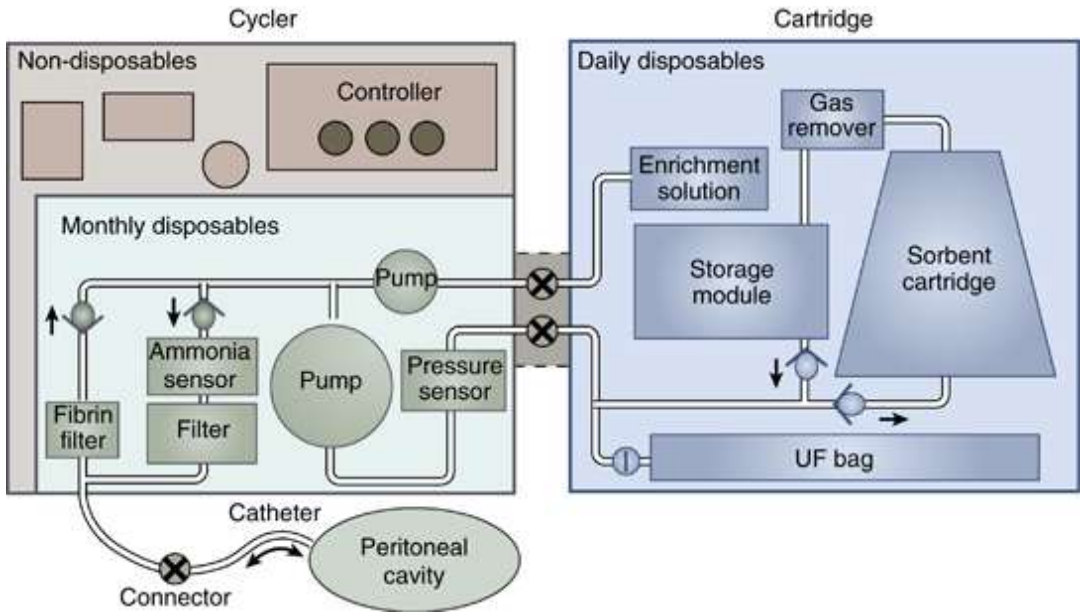
AWAK (Weight 3kg)

Daily replaceable assembly:

- Sorbent cartridge to regenerate spent dialysate
- Enrichment module containing electrolytes, lactate, and glucose to refresh regenerated dialysate

Monthly replaceable assembly:

- Ammonia sensor to monitor sorbent saturation
- Fibrin and bacterial filters



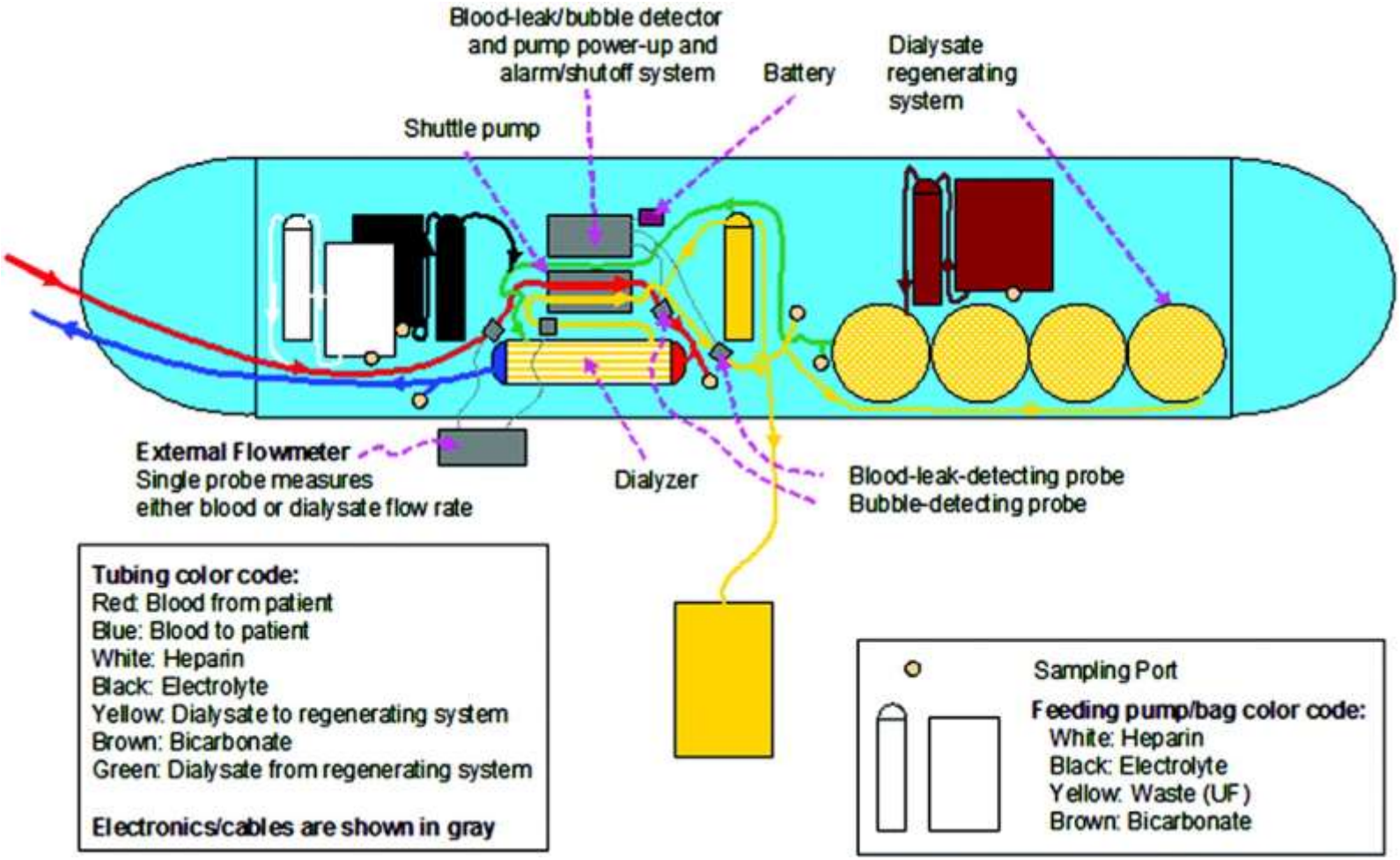
A study of 20 male patients using the AWAK for 4 to 24 hours demonstrated safety and efficacy with an average urea clearance of 31.4 mL/min

Continuous wearable Hemodialysis Devices

WAK
Wearable Artificial Kidney

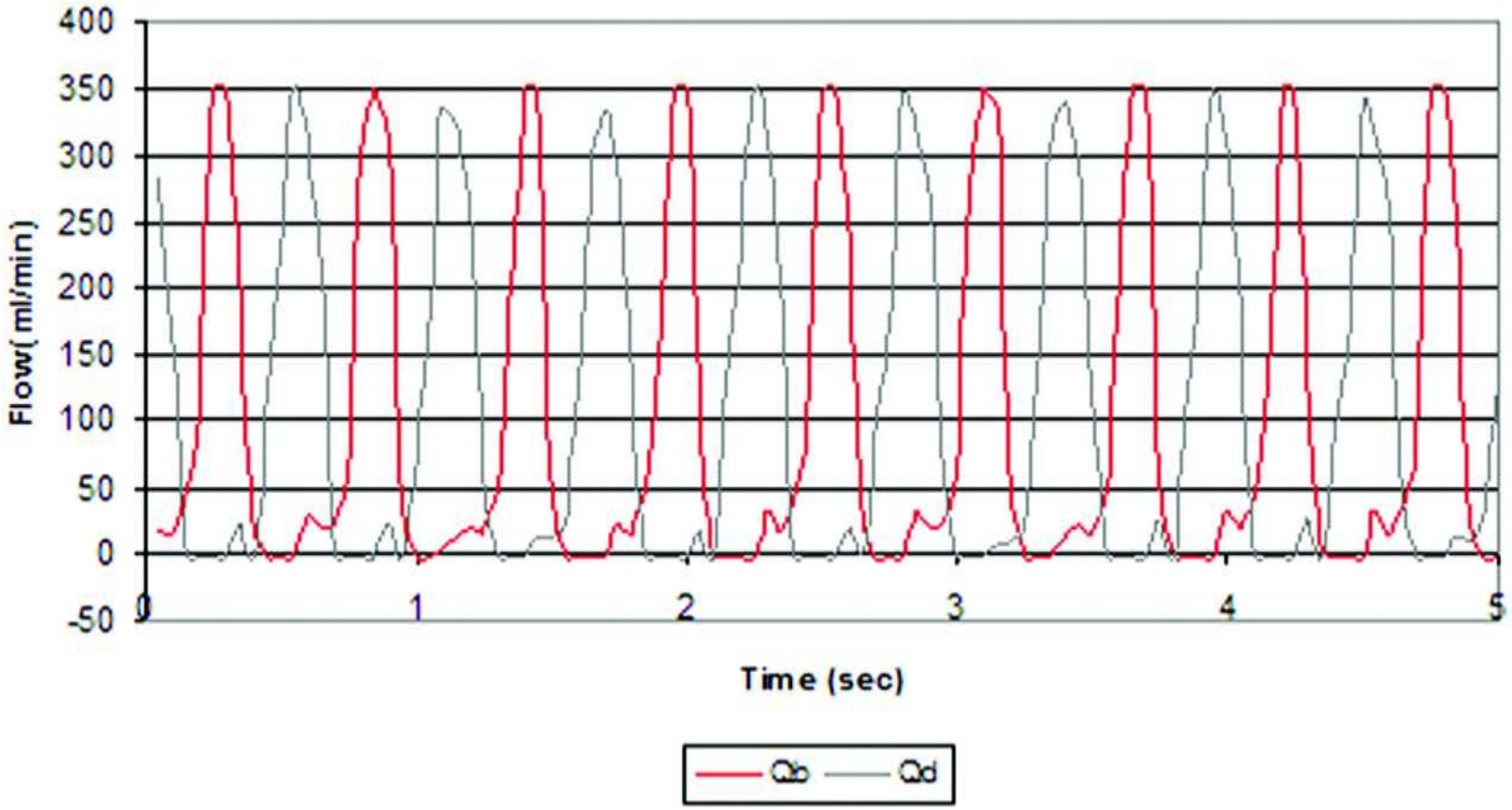
- Two 9-volt batteries
- 375mL of dialysate
- Blood volume 65mL
- Wearable with ~5Kg weight
- Double channel pulsatile counter phase flow
- Sorbent based with gas permeable plastic
- Daily exchange
- Blood access
- Anticoagulation needed

Schematics of the WAK. Blood drawn from a double lumen catheter (red) is anticoagulated with heparin from a reservoir (white) using a commercially available, battery-operated micro pump (ambIT, Sorenson, Salt Lake City, UT) and circulated through the blood ...



Gura V et al. CJASN 2009;4:1441-1448

The instantaneous blood flow waves of the WAK pump as recorded by flow-meter probes placed at the blood and dialysate tubing before the entrance to the pump



Gura V et al. CJASN 2009;4:1441-1448

CJASN

A wearable haemodialysis device for patients with end-stage renal failure: a pilot study

Andrew Davenport, Victor Gura, Claudio Ronco, Masoud Beizai, Carlos Ezon, Edmond Rambod

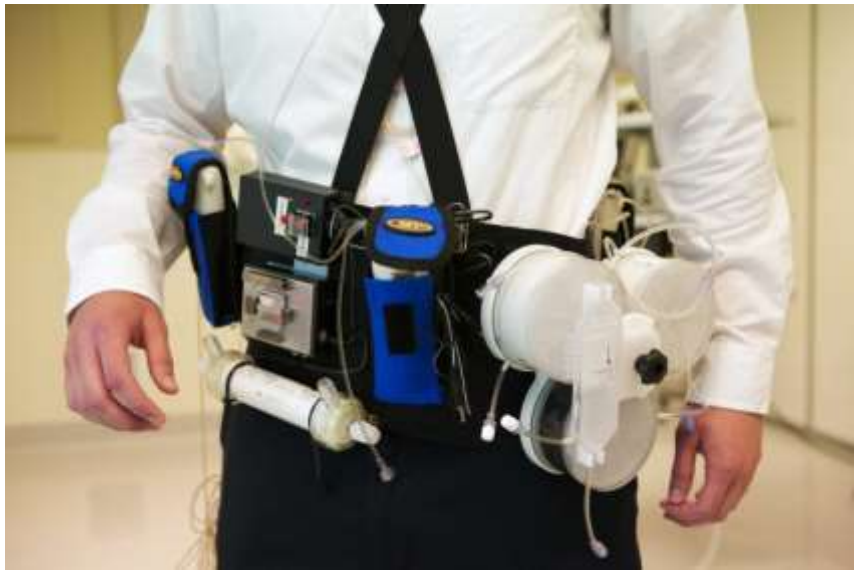
- 8 hemodialysis patients from UK with ESRD (5M,3F) Mean age 51·7 [SD 13·8] years
- Wearable hemodialysis device for **4–8 hrs**., Heparin (PTT 1.5-2.0)
- Mean Qb 58·6 (SD 11·7) mL/min,
- Mean Qd 47·1 (7·8) mL/min.
- **The mean plasma urea clearance rate was 22·7 (5·2) mL/min and the mean plasma creatinine clearance rate was 20·7 (4·8) mL/**min
- There were no important cardiovascular changes (BP, HR) and no adverse changes in serum electrolytes or acid-base balance.(Na, K, iCa, pH, Bicarb)
- There was no evidence of clinically significant hemolysis in any patient (Hct, LCD, Haptoglobulin)

Figure 2: A patient wearing the haemodialysis device

www.thelancet.com Vol 370 December 15, 2007

FDA approval of clinical trial

- Wearable Artificial Kidney (WAK device) was one of three products related to end-stage renal disease that were awarded a special fast-track to market status in April 2012 .
- In Feb, 2014 FDA approves trial for wearable artificial kidney
- **ClinicalTrials.gov Identifier:**
- NCT02280005



This is a prospective, interventional study designed to provide preliminary data on the human use of the WAK.

Up to 10 subjects via an indwelling tunneled catheter will be studied

JCI insight

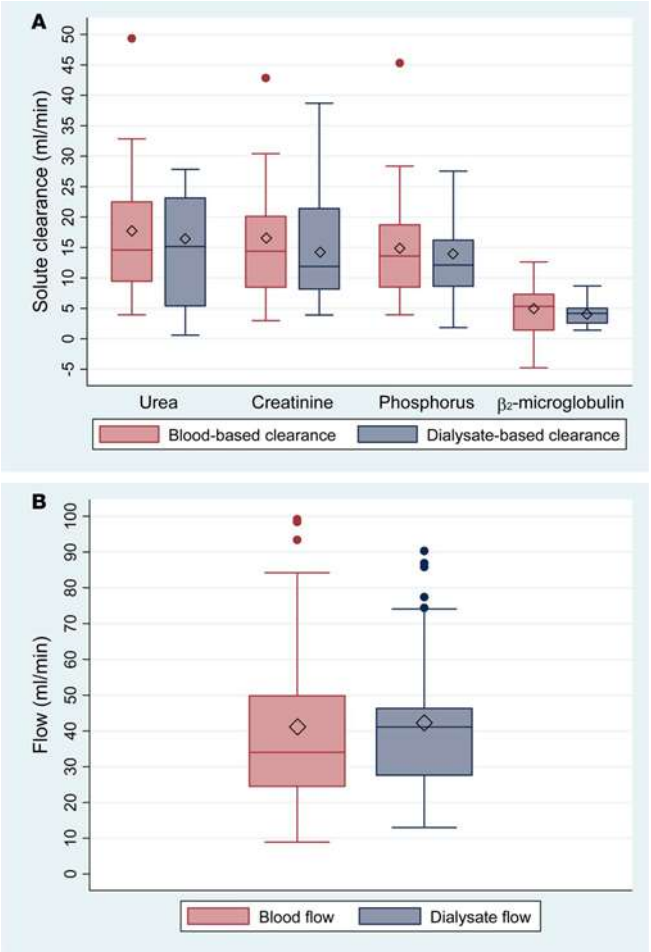
A wearable artificial kidney for patients with end-stage renal disease

Victor Gura,[1,2] Matthew B. Rivara,[3] Scott Bieber,[3] Raj Munshi,[3,4] Nancy Colobong Smith,[3,5] Lori Linke,[3] John Kundzins,[3] Masoud Beizai,[6] Carlos Ezon,[6] Larry Kessler,[3,7] and Jonathan Himmelfarb[3]

- **7 patients** **24 hours treatment**

- **Efficacy and safety of WAK**
  - Mean blood flow was 42 ± 24 ml/min
  - Mean dialysate flow was 43 ± 20 ml/min

- **Mean clearances over 24 hours:**
  - Urea 17 ± 10 ml/min
  - Creatinine 16 ± 8 ml/min
  - Phosphorus 15 ± 9 ml/min
  - β2-microglobulin 5 ± 4 ml/min



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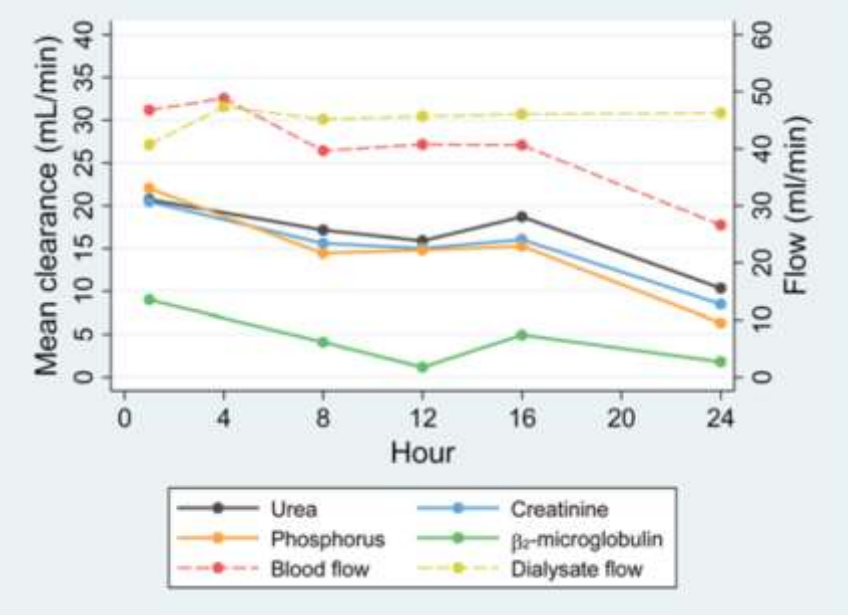
- Stable hemodynamics and electrolytes
- Well tolerated and effective uremic solute clearance
- In one subject, treatment was discontinued due to clotting after four hours.
- In a second subject, treatment was discontinued due to discoloration of dialysate observed after 10 hours.
- The trial was stopped after the 7th subject due to device-related malfunctions that included excessive CO2 bubbles in the dialysate, variable blood and dialysate flows.
- Redesign and re-manufacturing of the WAK prototype will be required prior to additional human studies.



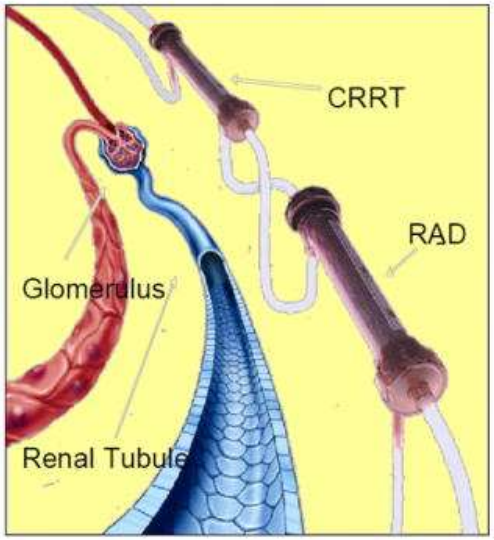
Mean small solute and middle molecule clearances, blood flow, and dialysate flow over the 24-hour WAK treatment period

Bio-artificial and implantable artificial kidney

Renal tubule cell assistance device (RAD) and the first bio-artificial kidney

- **The first RAD was developed by Humes and colleagues at the University of Michigan in 1997.**
- **The renal tubule assist device (RAD) is composed of a conventional hemofilter lined by monolayers of renal cells**
- **The RAD was incorporate into extracorporeal circulation system in <u>series</u> by a conventional hemofilter with structural construction of circuit mimicking functional nephron**

	Current Treatment	RBT
Waste Control	✓	✓
Fluid Balance	✓	✓
Immune Modulation		
Host defense system		✓
Antigen presentation		✓
Cytokine production		✓
Metabolic/ endocrine functions		
Hormone production		✓
Vitamin production		✓
Ca, Phos homeostasis		✓

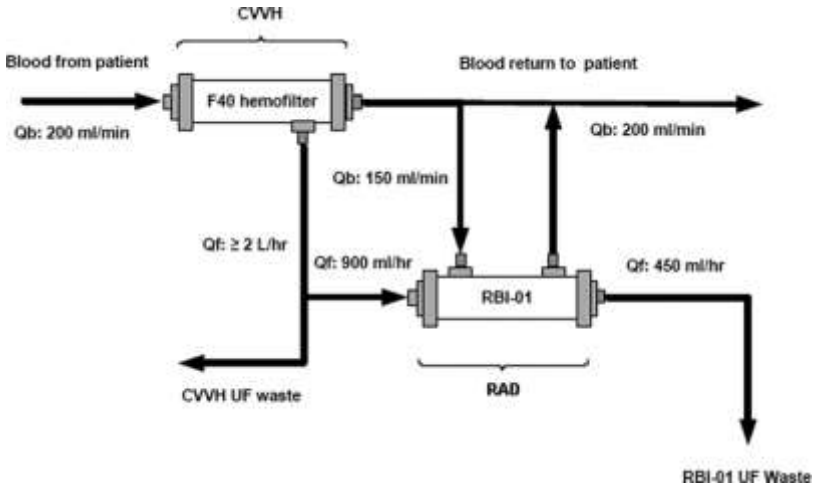


Song JH, Humes HD: Renal cell therapy and beyond. Semin Dial 22:603-9. 2009

Efficacy and Safety of Renal Tubule Cell Therapy for Acute Renal Failure

- Phase II, multicenter, randomized, controlled, open-label trial

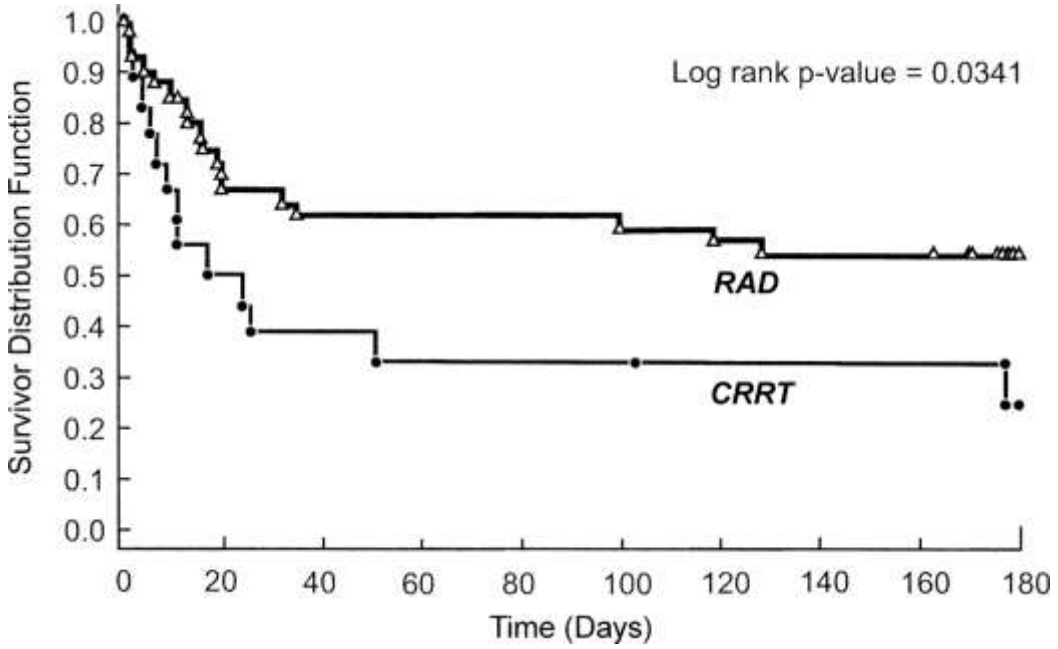
- 58 patients
- 40—CRRT + RAD
- 18—CRRT alone



Tumlin J et al. JASN 2008;19:1034-1040

Kaplan-Meier estimates of survival between patients in the RAD and conventional CRRT groups.

At day 28, the mortality rate was 33%in the RAD group and 61% in the CRRT group.

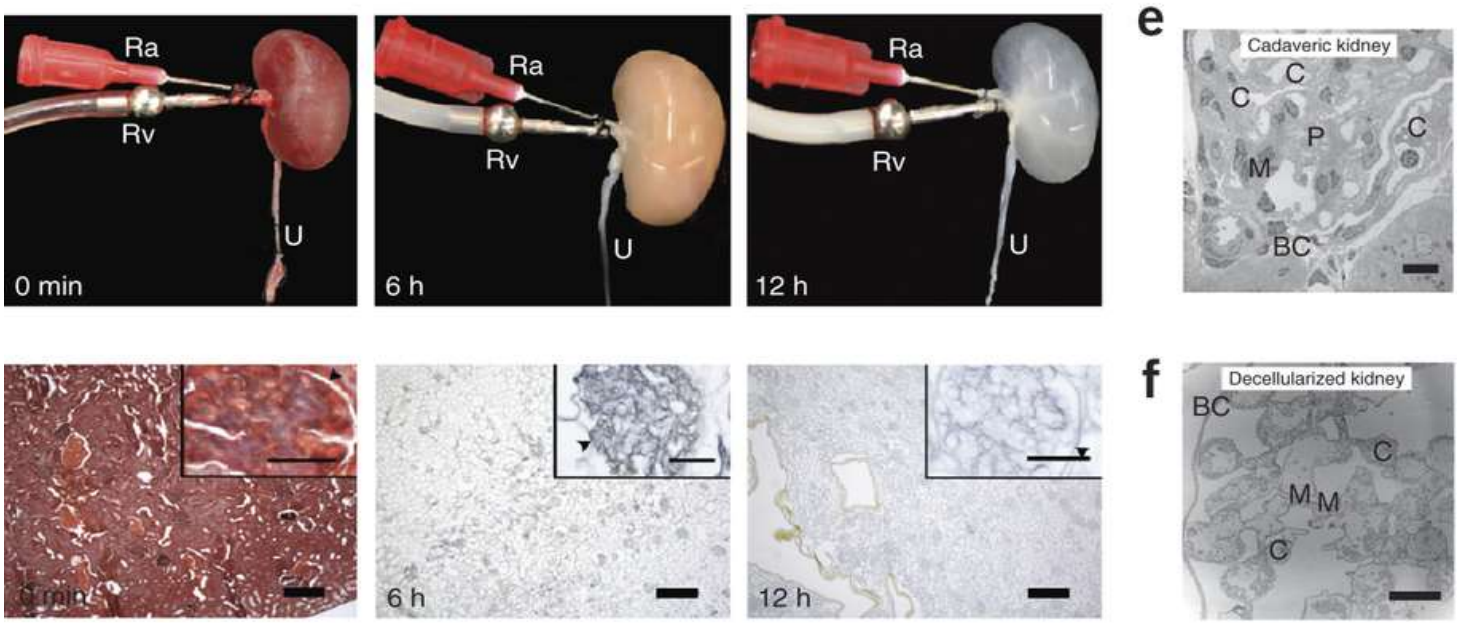


Tumlin J et al. JASN 2008;19:1034-1040

Regeneration and experimental orthotopic transplantation of a Bioengineered kidney

Nature Medicine Volume: 19, Pages: 646–651 (2013)

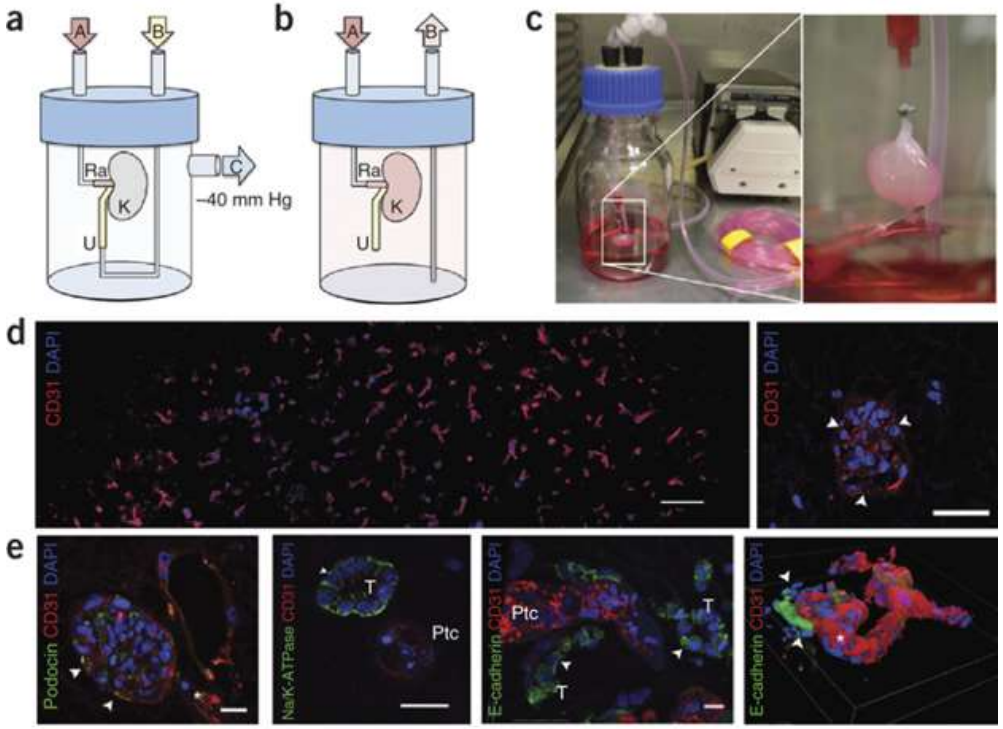
Perfusion Decellularization of cadaveric kidneys



Using SDS perfusion, decellularization of rat kidney led to acellular scaffolds with vascular, cortical and medullary architecture, a collecting system and ureters.

Preservation of extracellular matrix proteins in the absence of cells.

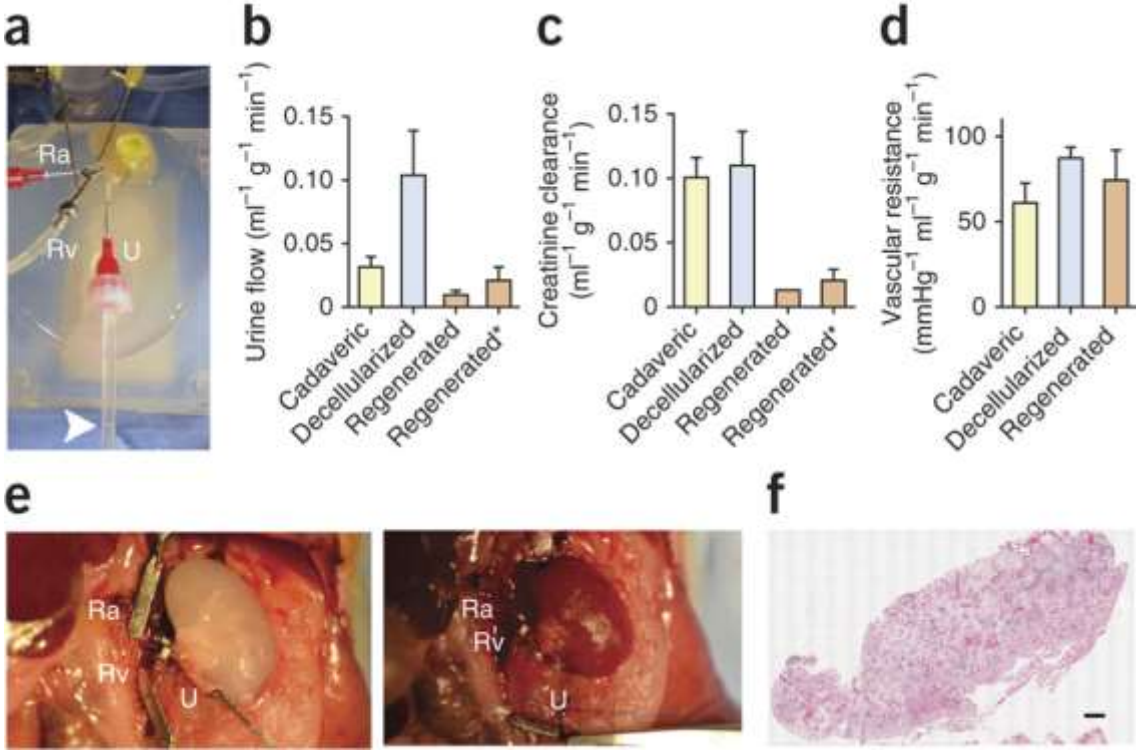
Recellularization of acellular kidney scaffolds



Rat kidney scaffolds were seeded with epithelial and endothelial cells and perfused these cell-seeded constructs in a whole-organ bioreactor.

When cultured on cell-culture plastic after isolation, 8% of adherent cells expressed podocin, indicating a glomerular epithelial phenotype, 69% expressed Na/K-ATPase, indicating a proximal tubular phenotype, and 25% expressed E-cadherin, indicating a distal tubular phenotype

In vitro function of acellular and regenerated kidneys; Orthotopic transplantation of regenerated kidneys

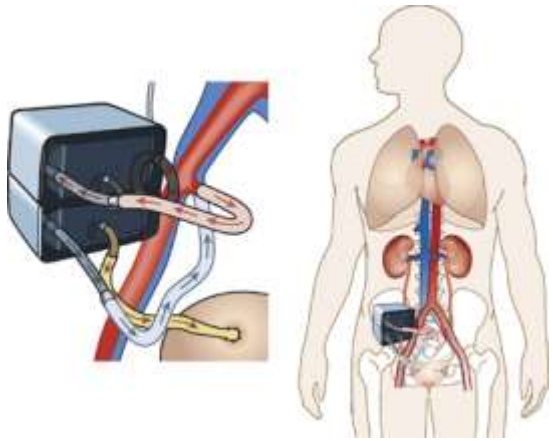


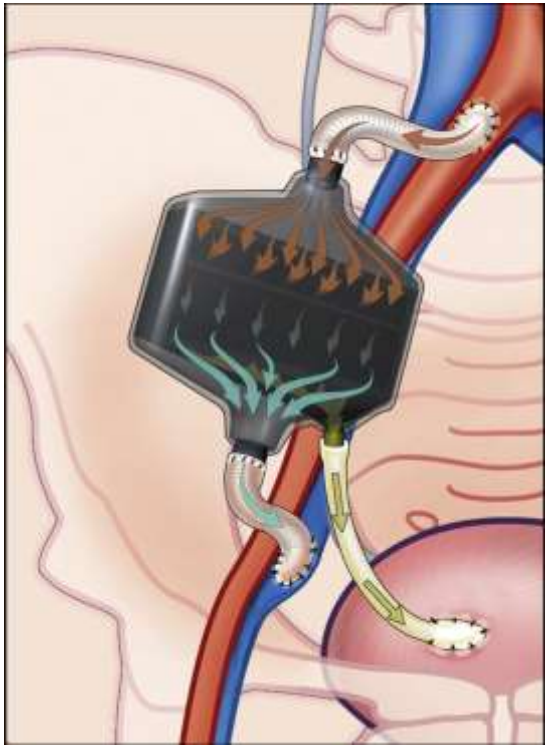
The resulting grafts produced rudimentary urine in vitro.

When transplanted in an orthotopic position in rat, the grafts were perfused by the recipient's circulation and produced urine through the ureteral conduit in vivo.

Implantable Artificial Kidney

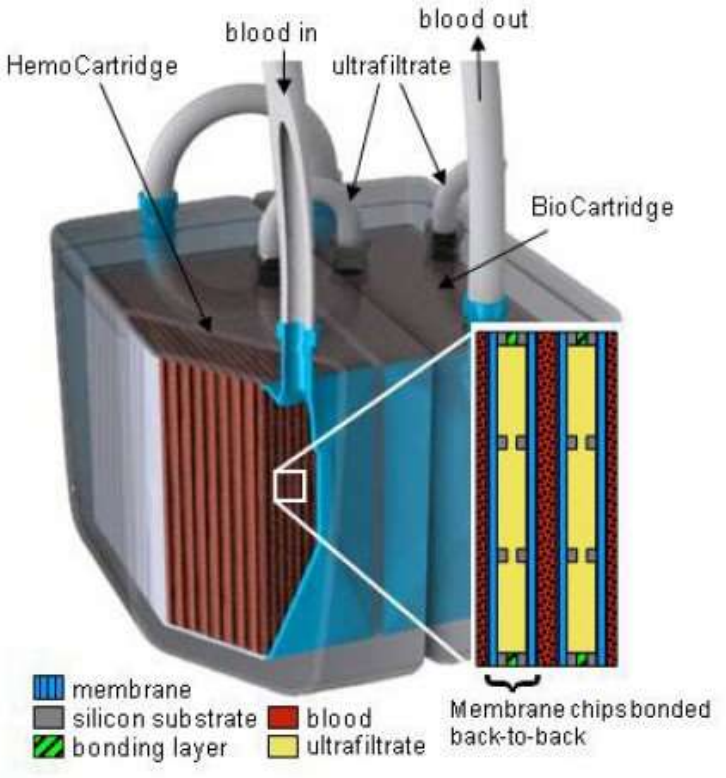
The IAK
Vanderbilt University Medical Center
and
USCD

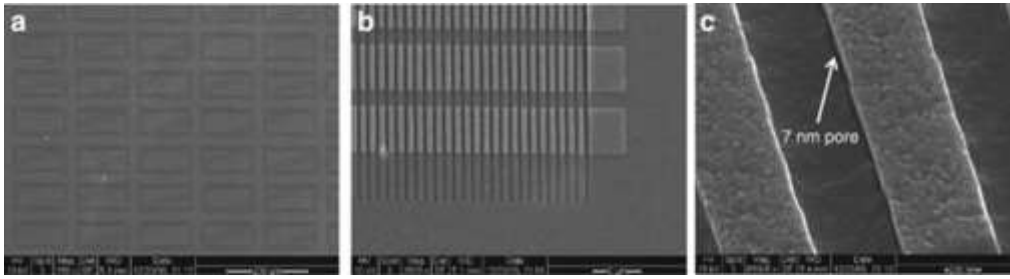


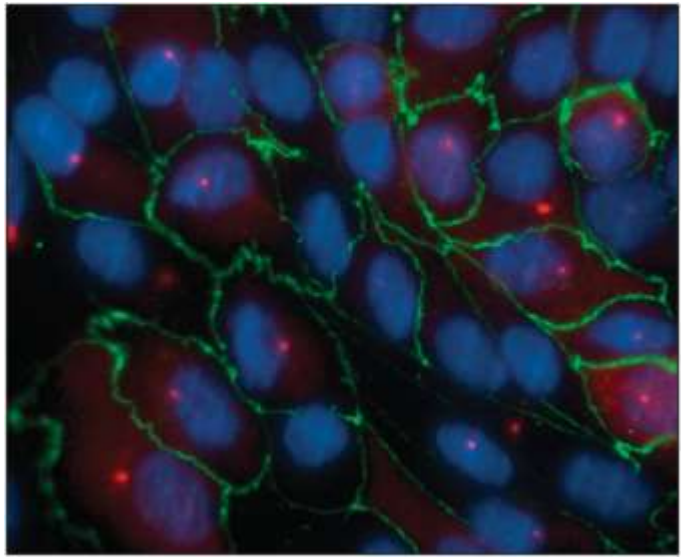


Implantable Artificial Kidney

Implantable Artificial Kidney





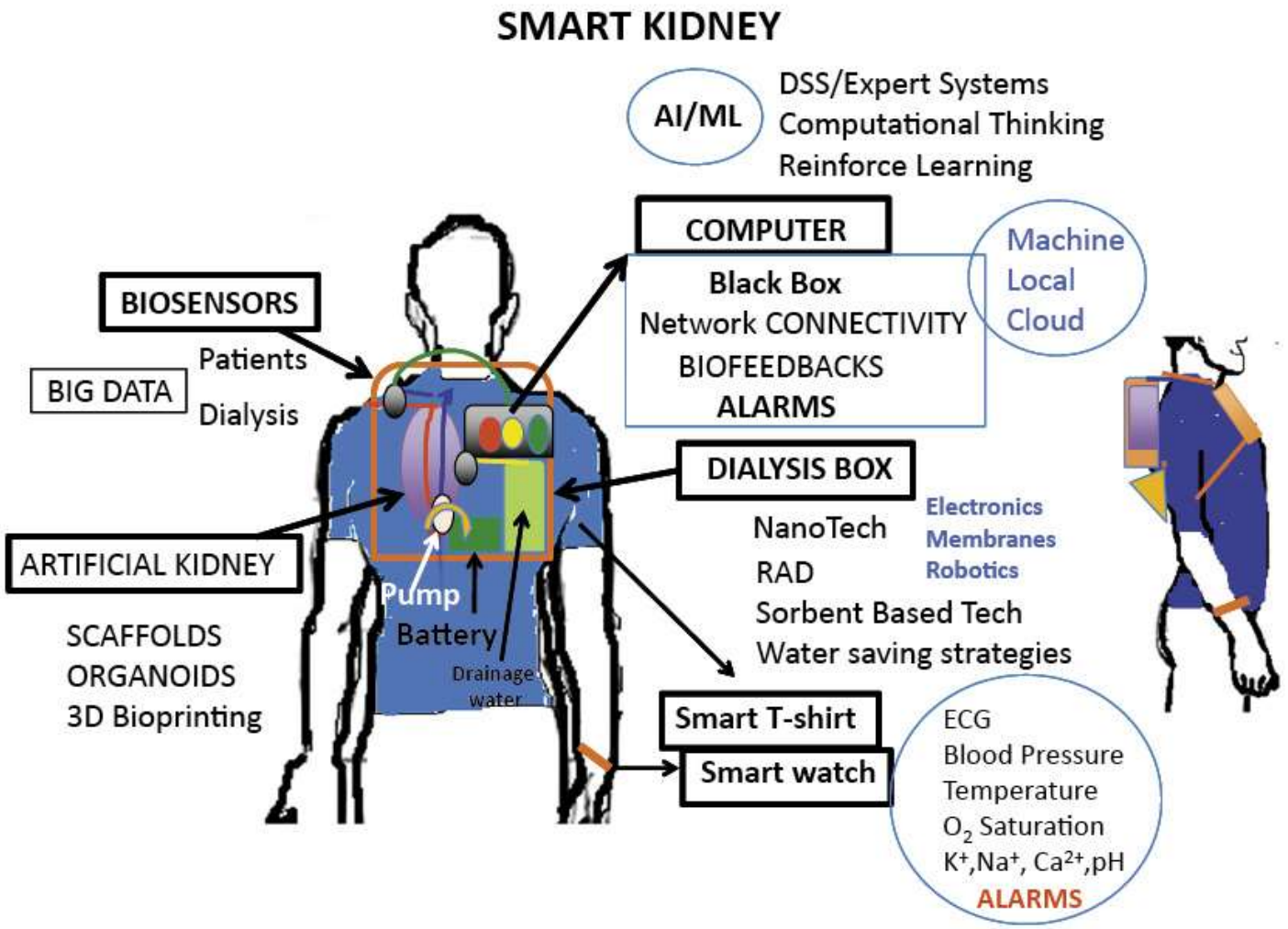


Comparison of WAKs and IAK

	AWAK	WAK	IAK
Weight	<2kg	<5kg	~500g
Power	Battery	Battery	None (CV Pressure)
Fluid needs	~2L /treatment	500mL per treatment	Patient drinks electrolytes
Stages of Development	Human Trials	FDA Clinical Trials	Animal models
Strengths	Bloodless Portable High clearance	Portable Low UF rate	Implantable Easy for patient
Limitations	Every 7 hours cartridge exchange	Clotting and bleeding issues	Repeat invasive procedures

Am J Kidney Dis. 72(5): 745-751.
doi: 10.1053/j.ajkd.2018.06.005

Patients need ‘SMART KIDNEY’



https://doi.org/10.1159/000492932

What is Xenotransplantation

- Transplantation of living cells, tissues, or organs from one species to another.

Original Article

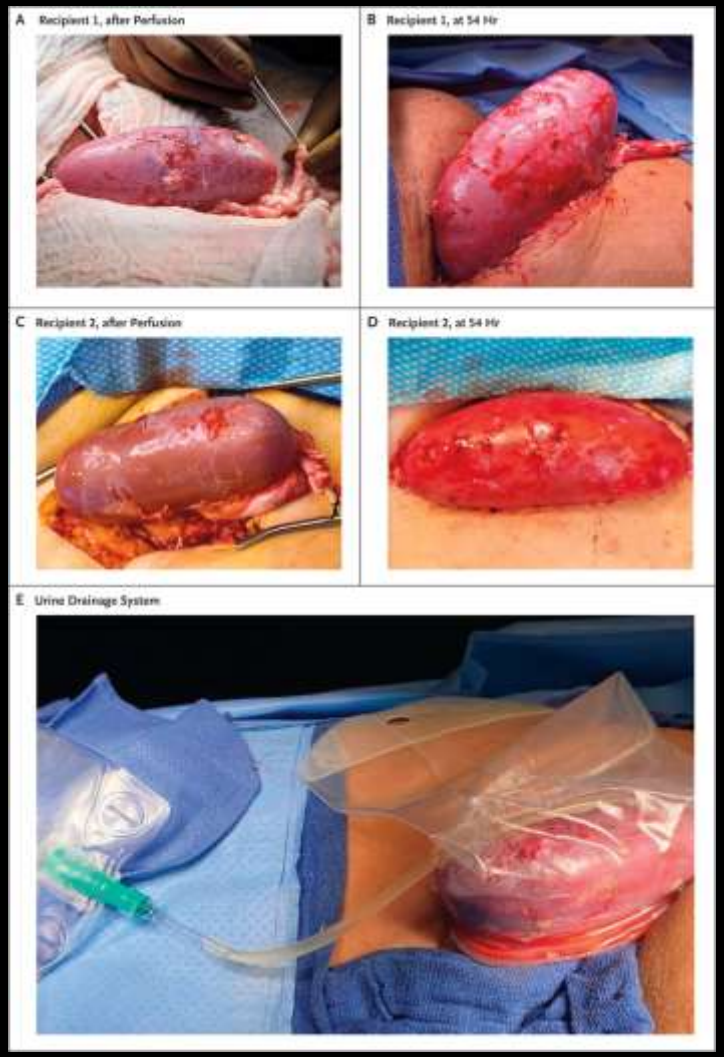
Results of Two Cases of Pig-to-Human Kidney Xenotransplantation

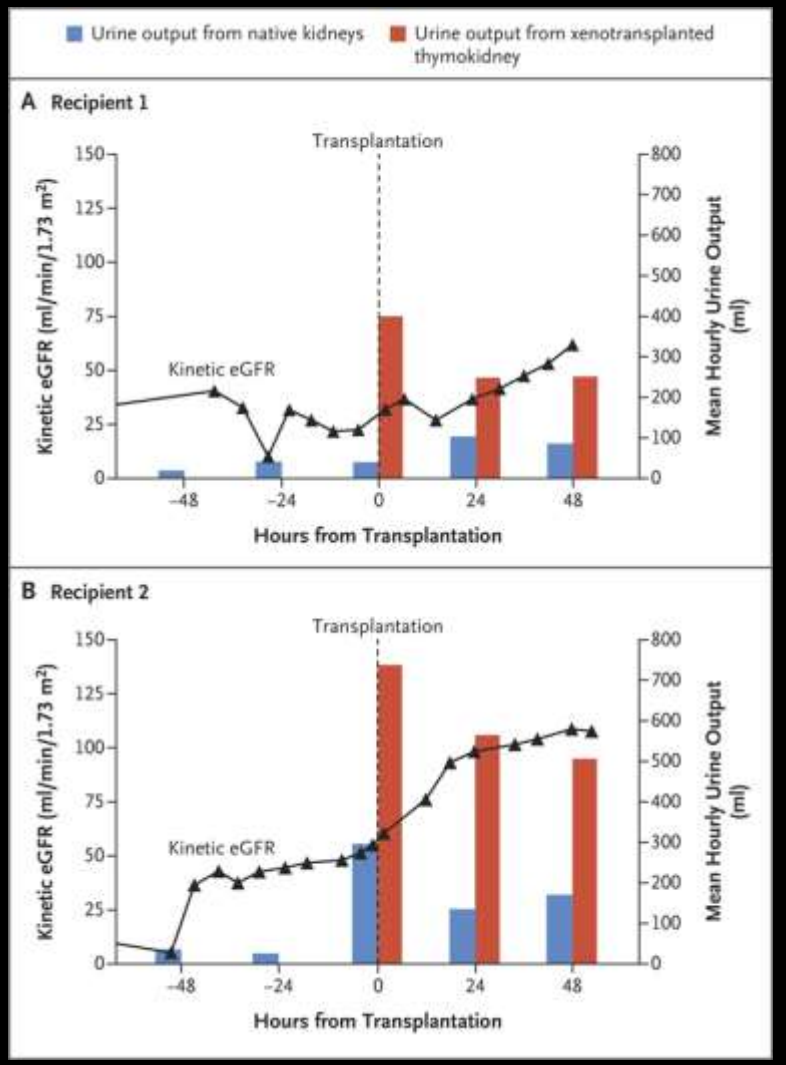
Robert A. Montgomery, M.D., D.Phil., Jeffrey M. Stern, M.D., Bonnie E. Lonze, M.D., Ph.D., Vasishta S. Tatapudi, M.D., Massimo Mangiola, Ph.D., Ming Wu, M.D., Elaina Weldon, M.S.N., A.C.N.P.-B.C., Nikki Lawson, R.N., Cecilia Deterville, M.S., Rebecca A. Dieter, Pharm.D., B.C.P.S., Brigitte Sullivan, M.B.A., Gabriella Boulton, B.A., Brendan Parent, J.D., Greta Piper, M.D., Philip Sommer, M.D., Samantha Cawthon, B.S., Erin Duggan, M.D., David Ayares, Ph.D., Amy Dandro, M.S., Ana Fazio-Kroll, Ph.D., Maria Kokkinaki, Ph.D., Lars Burdorf, M.D., Ph.D., Marc Lorber, M.D., Jef D. Boeke, Ph.D., Harvey Pass, M.D., Brendan Keating, Ph.D., Adam Griesemer, M.D., Nicole M. Ali, M.D., Sapna A. Mehta, M.D., and Zoe A. Stewart, M.D., Ph.D.

N Engl J Med
Volume 386(20):1889-1898
May 19, 2022

The NEW ENGLAND JOURNAL of MEDICINE

Mean Hourly Urine Output and Kinetic Estimated Glomerular Filtration Rate (eGFR





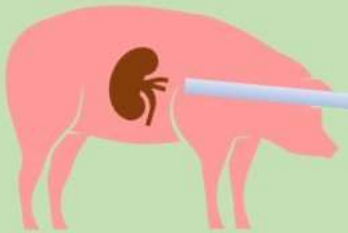
Montgomery RA et al. N Engl J Med2022;386:1889-1898

The NEW ENGLAND JOURNAL of MEDICINE

What were the outcomes of the first clinical-grade porcine kidney xenotransplant ?

#NephJC

The donor pig



Novel cross-match

10 gene modifications

Free of specified pathogens

The decedent recipient

Both pig kidneys were transplanted

Bilateral native nephrectomies

Urine produced by one kidney only
No creatinine excretion

Outcomes

No hyperacute rejection
Histologic features of TMA on POD1

Successful cross-match technique

No life-threatening intraoperative complications

No porcine antigens detected in decedent blood

Successful execution of best practices for safe clinical trials

Conclusion: Critical safety and feasibility questions in xenotransplantation were addressed by using a novel pre-clinical human model, under significant regulatory oversight.

TMA – thrombotic microangiopathy; POD – post-operative day

Locke, et al, 2021
Visual abstract by:
Namrata Parikh, DNB
@NamrataYParikh

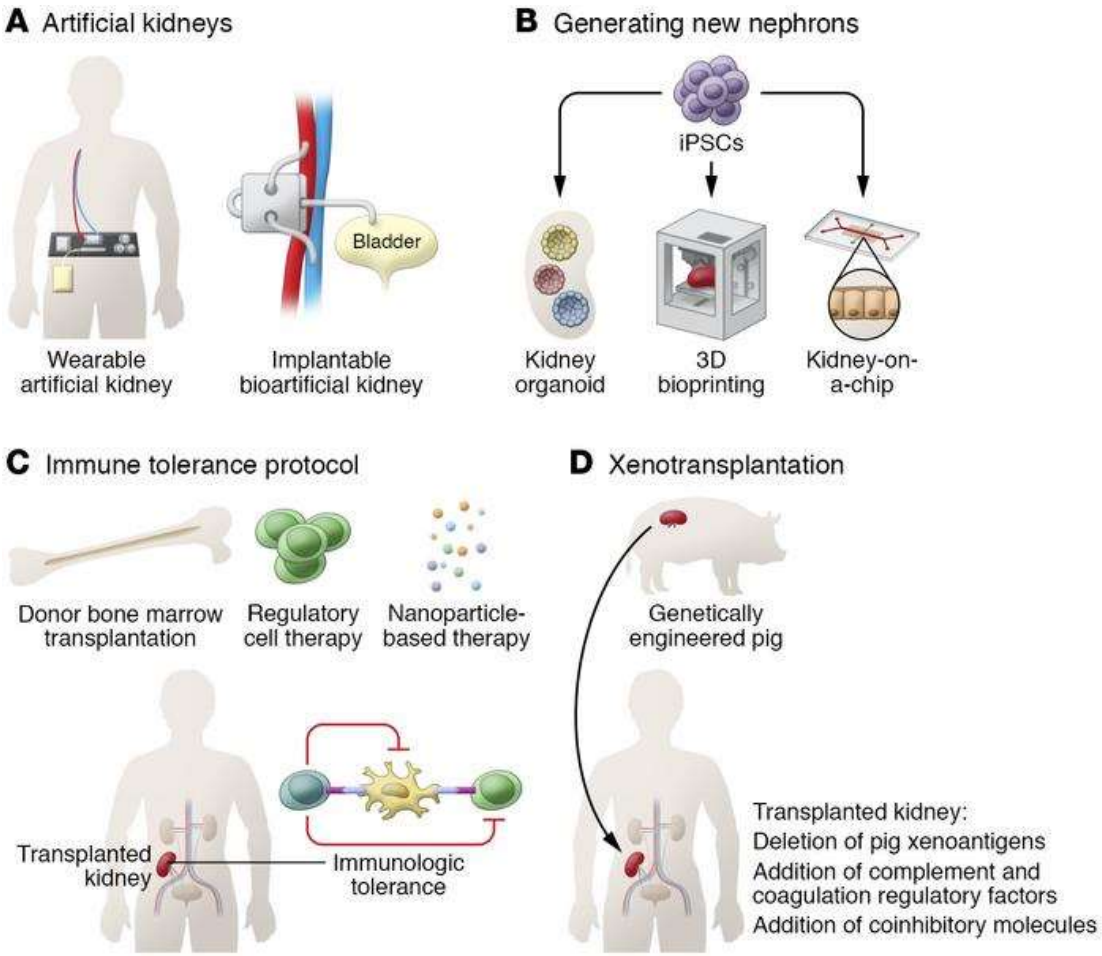
Waitlist for Kidney Transplantation

- As of 8/21/2022:
- 105,761 Americans currently on the waiting list for a lifesaving organ transplant
- >91,000 need a kidney
  - ~17,000 people receive deceased donor kidney
  - ~5300 living donors
- Every day 12 people die waiting for a kidney.

Waiting list candidates as of 08/21/2022	
All	105,761
Kidney	89,896
Pancreas	861
Kidney/Pancreas	1,916
Liver	11,081
Intestine	196
Heart	3,358
Lung	998
Heart/Lung	30

https://optn.transplant.hrsa.gov/data/

Next-generation approaches for ESRD



J Clin Invest. 2022;132(7):e159308. https://doi.org/10.1172/JCI159308.

Thank you

EVALUATION/CERTIFICATE

Evaluation of this activity is integral to the CME process. Please complete the evaluation at https://www.surveymonkey.com/r/E6762eval. This link will be available through **September 13, 2022**. Please note that if you do not complete this evaluation through the provided link, your credit certificate issuing will be delayed. A certificate will be emailed to you within 4 weeks if the evaluation has been completed. For information specific to continuing medical education credit, call Continuing Education, at (717) 531-6483 or email ContinuingEd@pennstatehealth.psu.edu

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