DIALYSIS

Future Options...

Ο φορητός ή εμφυτεύσιμος νεφρός αποτελεί τη λύση του μέλλοντος?

Ιωάννης Γριβέας, MD, PhD
Νεφρολόγος

athens-NEPHROLOGY

nature reviews nephrology
https://doi.org/10.1038/s41581-024-00820-6

Consensus statement

Check for updates

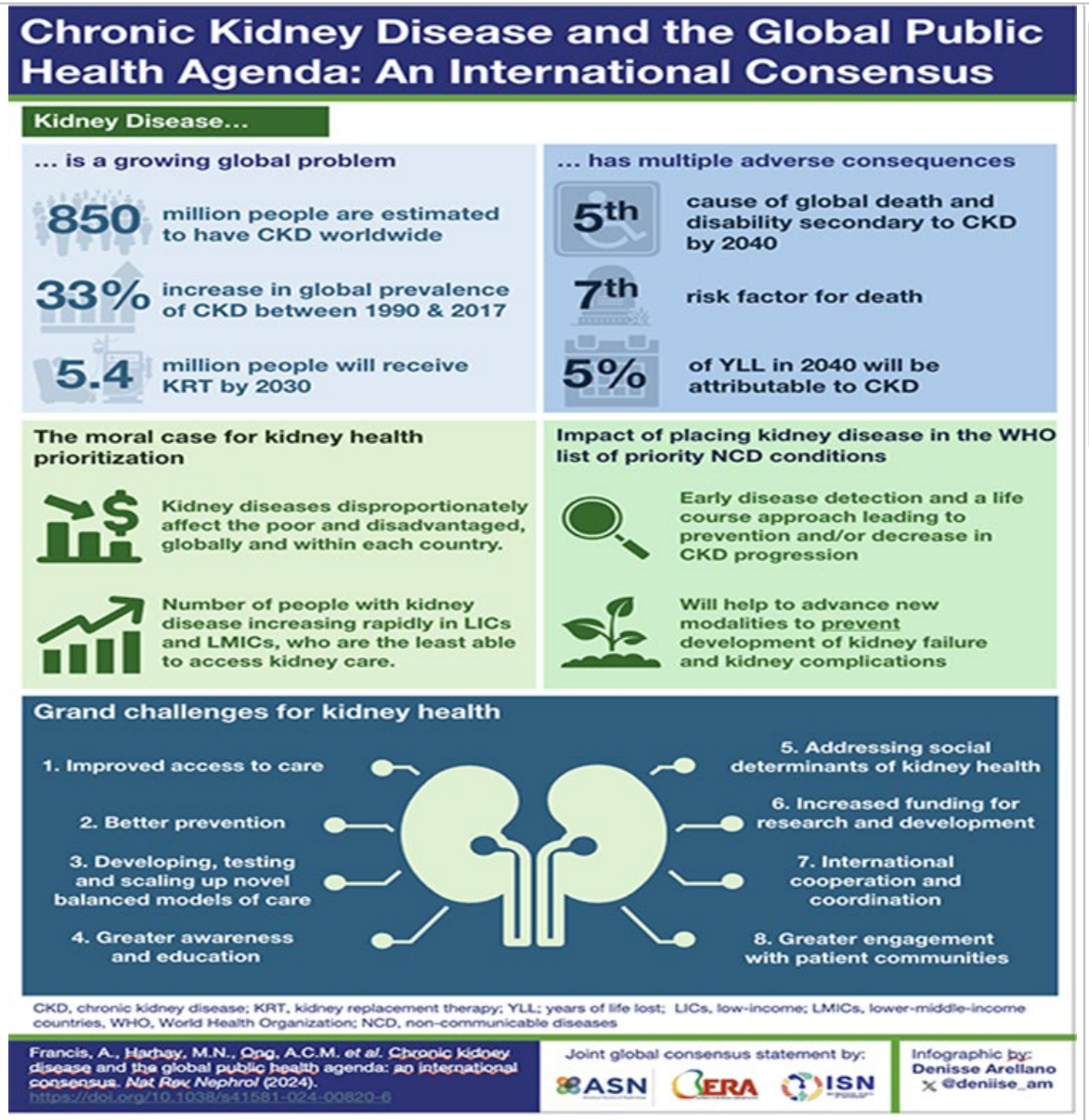
Chronic kidney disease and the global public health agenda: an international consensus

Anna Francis[1], Meera N. Harhay[2,3], Albert C. M. Ong[4], Sri Lekha Tummalapalli[5,6], Alberto Ortiz[7], Agnes B. Fogo[8], Danilo Fliser[9], Prabir Roy-Chaudhury[10], Monica Fontana[11], Masaomi Nangaku[12], Christoph Wanner[13], Charu Malik[14], Anne Hradsky[14], Dwomoa Adu[15], Sunita Bavanandan[16], Ana Cusumano[17], Laura Sola[18], Ifeoma Ulasi[19], Vivekanand Jha[20,21,22] ✉, American Society of Nephrology*, European Renal Association* & International Society of Nephrology*

Abstract

Early detection is a key strategy to prevent kidney disease, its progression and related complications, but numerous studies show that awareness of kidney disease at the population level is low. Therefore, increasing knowledge and implementing sustainable solutions for early detection of kidney disease are public health priorities. Economic and epidemiological data underscore why kidney disease should be placed on the global public health agenda — kidney disease prevalence is increasing globally and it is now the seventh leading risk factor for mortality worldwide. Moreover, demographic trends, the obesity epidemic and the sequelae of climate change are all likely to increase kidney disease prevalence further, with serious implications for survival, quality of life and health care spending worldwide. Importantly, the burden of kidney disease is highest among historically disadvantaged populations that often have limited access to optimal kidney disease therapies, which greatly contributes to current socioeconomic disparities in health outcomes. This joint statement from the International Society of Nephrology, European Renal Association and American Society of Nephrology, supported by three other regional nephrology societies, advocates for the inclusion of kidney disease in the current WHO statement on major non-communicable disease drivers of premature mortality.

Sections

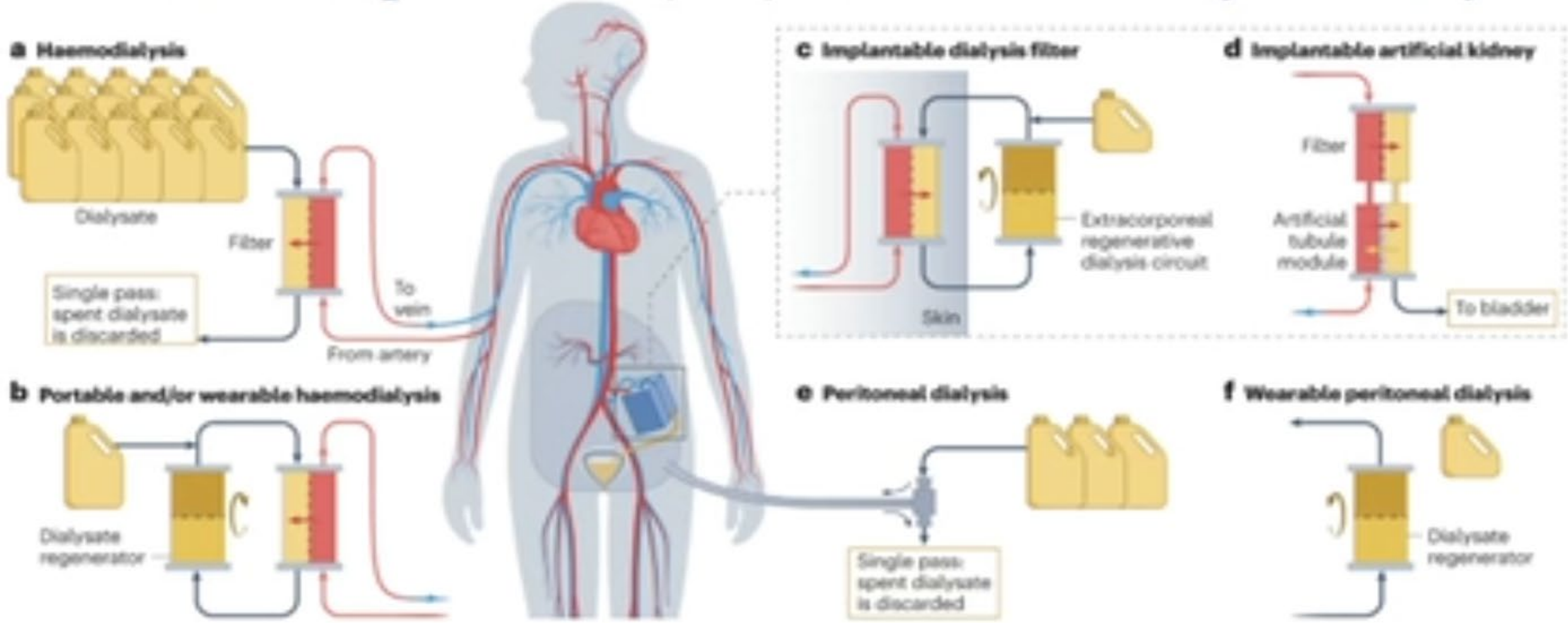


Dialysis and Transplant Limitations

- Non-physiological
- Tethered
- Utilities
- Expensive

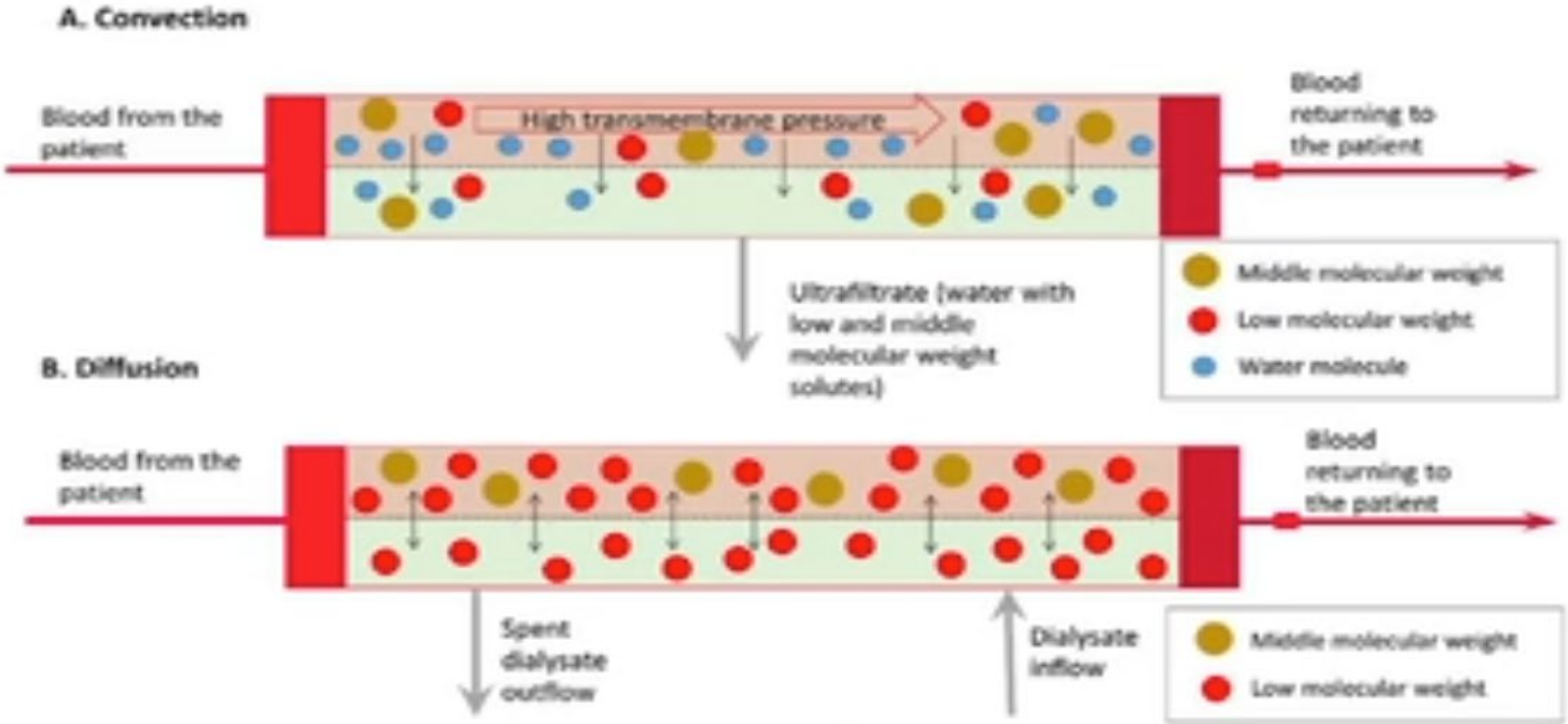
- Scarcity
- Immunosuppression

Wearable/Implantable (Bio)Artificial Kidney or Dialysis



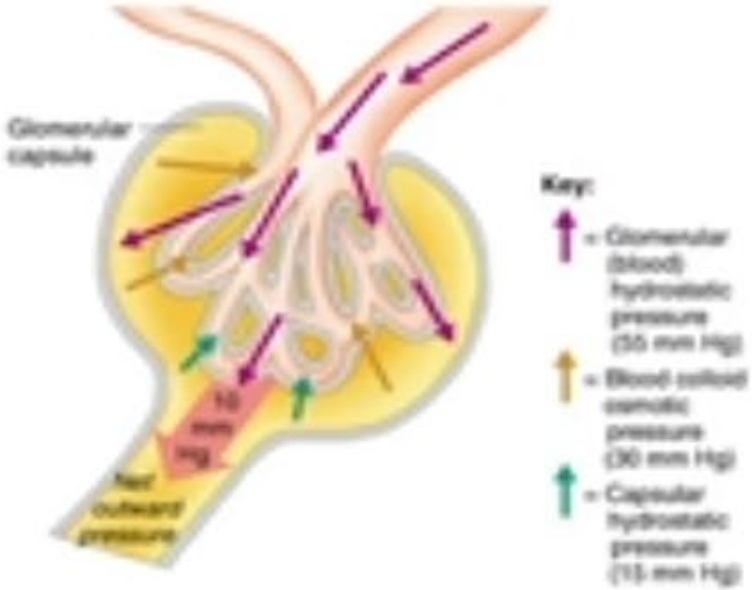
Ramada et al. Nat Rev Nephrol 19, 481–490 (2023).

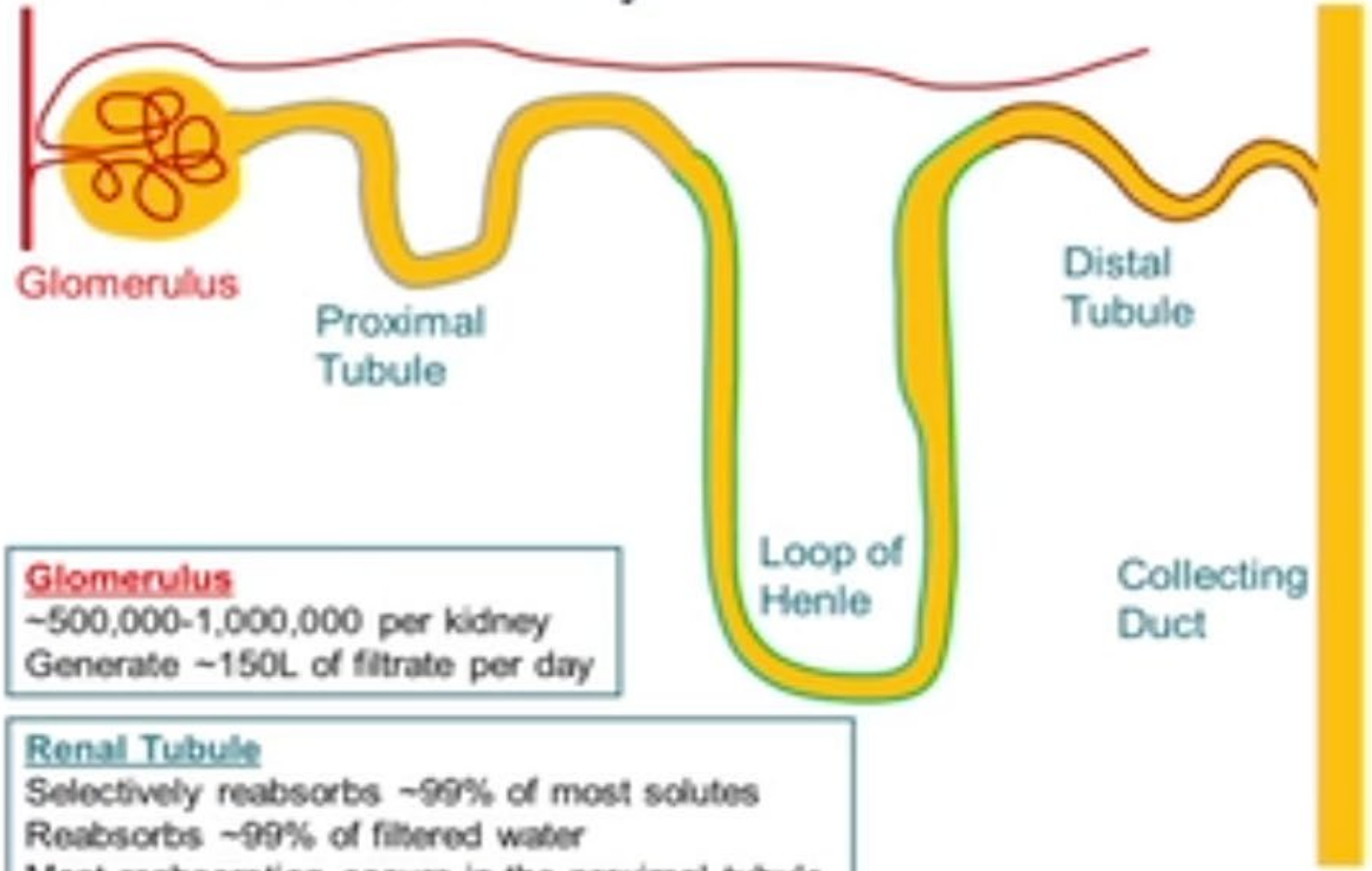
Principles of Membrane Solute Removal



Fiaccadori et al. Clin Nutr. 2021 Apr;40(4):1644-1668

Filtration in Kidney





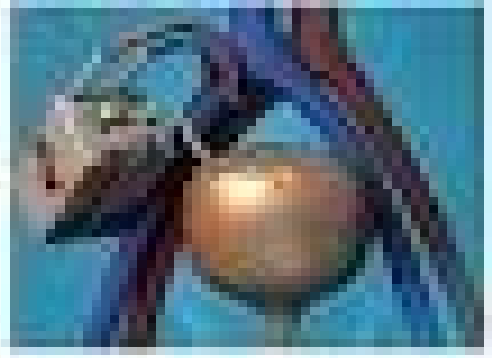
Glomerulus
~500,000-1,000,000 per kidney
Generate ~150L of filtrate per day

Renal Tubule
Selectively reabsorbs ~99% of most solutes
Reabsorbs ~99% of filtered water
Most reabsorption occurs in the proximal tubule

https://www.letstalkmed.com/glomerular-filtration-rate

Proximal tubule functional characterization

- Cell viability
- Glucose reabsorption
- Regulated Kidney Injury Molecule 1 expression
- Glutathione synthesis
- Ammoniagenesis
- Vitamin D biotransformation (cytochrome P450)
- Polarized transporter expression
- Organic anionic secretion
- Organic cationic secretion

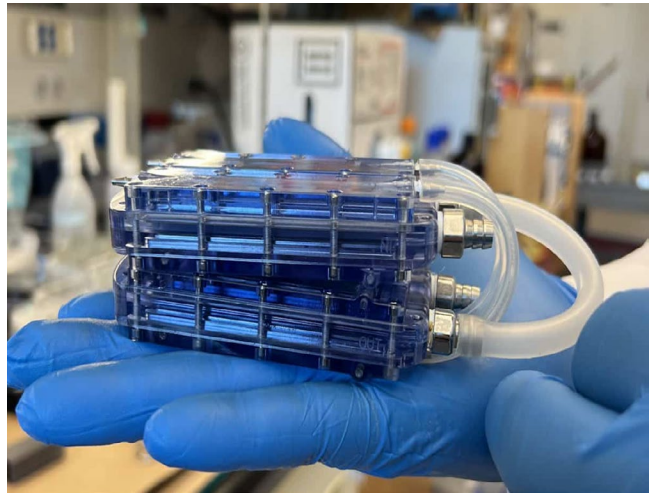


1st generation
Portable
Artificial
Kidney (PAK)
10-35 kg

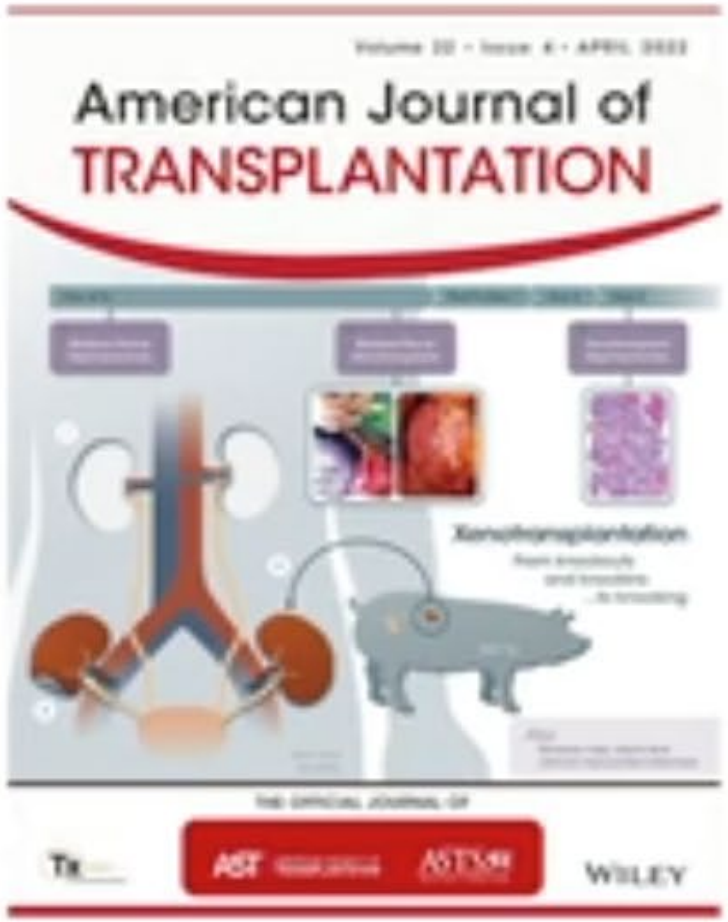
2nd generation
PAK
1.5-10 kg

Wearable
Artificial
Kidney (WAK)
<1.5 kg

(Implantable)
Bioartificial
Kidney (BAK)



Current Landscape – Implantable (Bio)Artificial Kidneys



Porrett et al. (University of Alabama, Birmingham)

ASN Kidney Week 2019: Uzarski et al. (Miromatrix Medical)

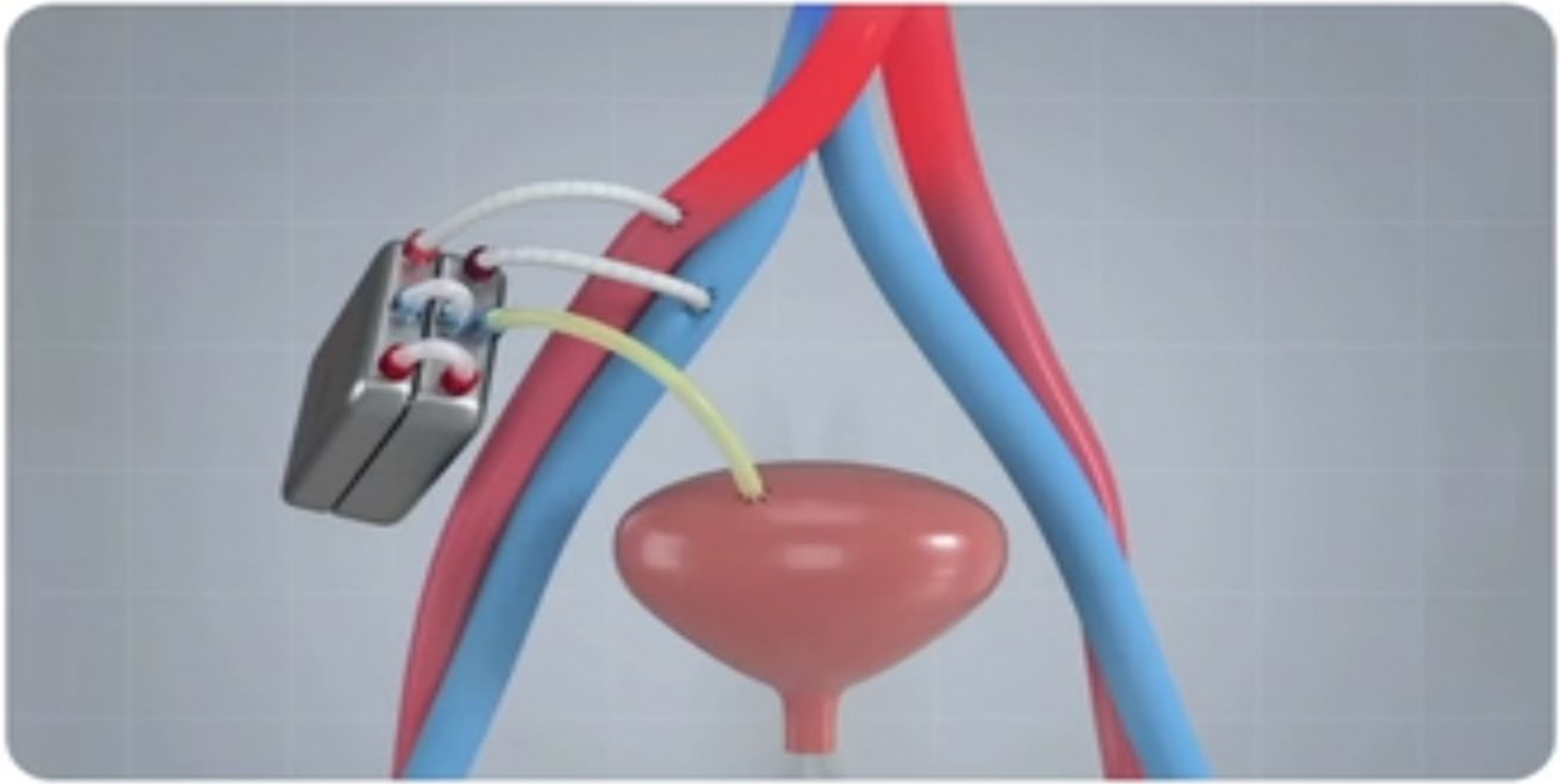
LIMITED DIALYSIS

LESS THAN 10% REMOVAL OF TOXINS

PROTEINS BOUND DIFFICULT

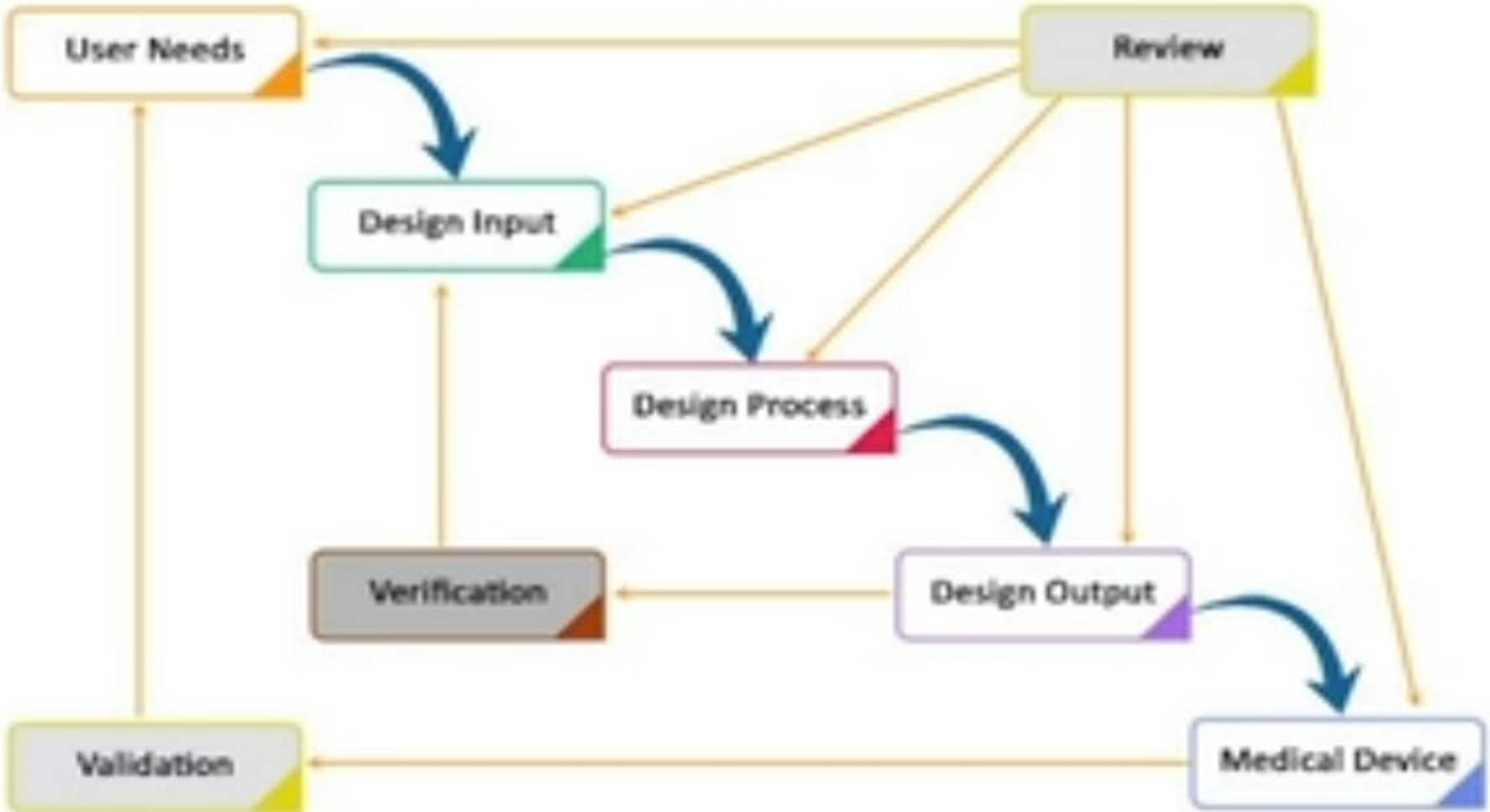
CONSTANT STATE OF INFLAMMATION…

Our Goal - Implantable Bioartificial Kidney (iBAK)



Engineering Approach – Mars Rover Example

Waterfall Design Process for Medtech Development



Patient Preferences = User Needs

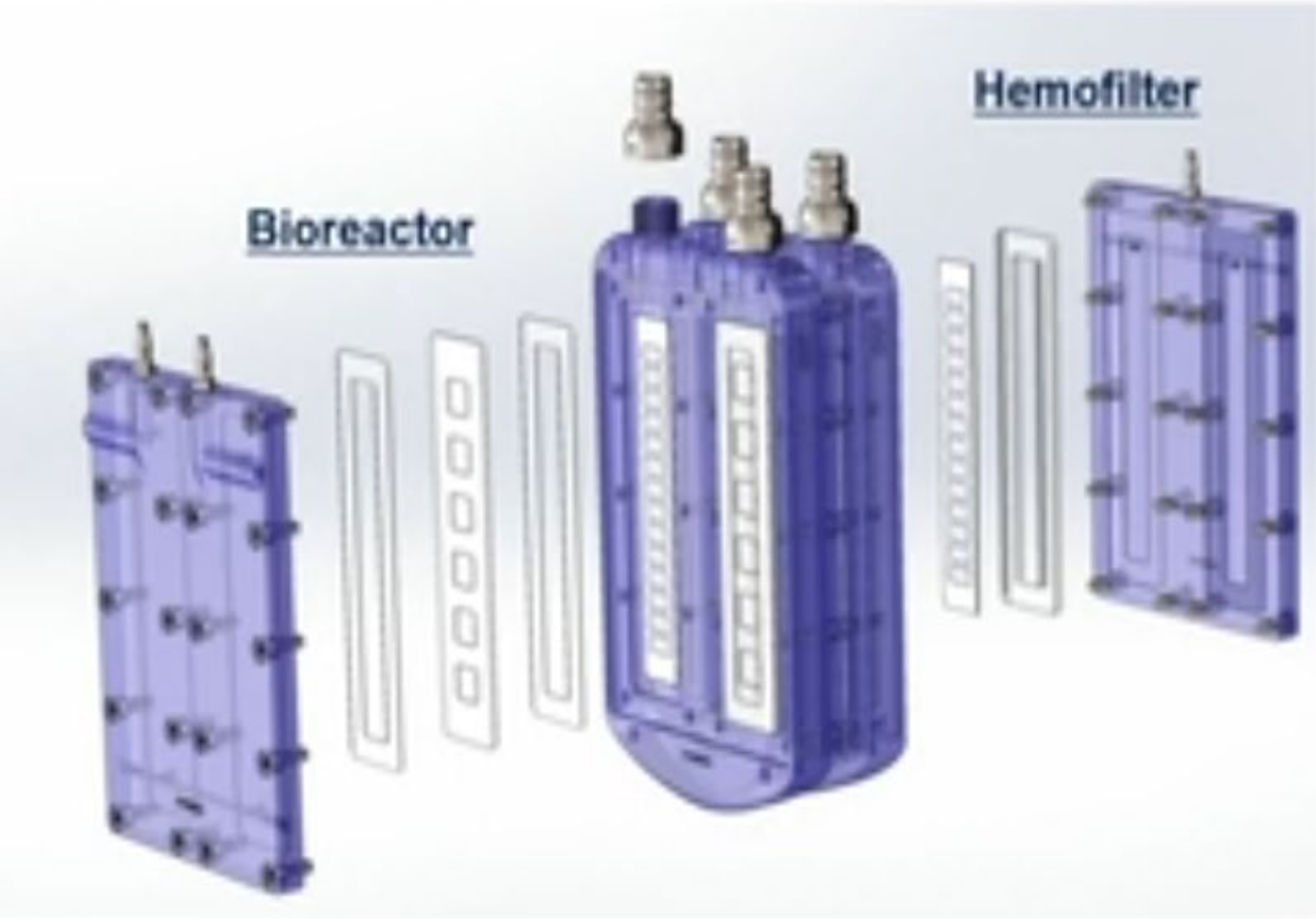
Patient Preference Trade-Offs for Next-Generation Kidney Replacement Therapies

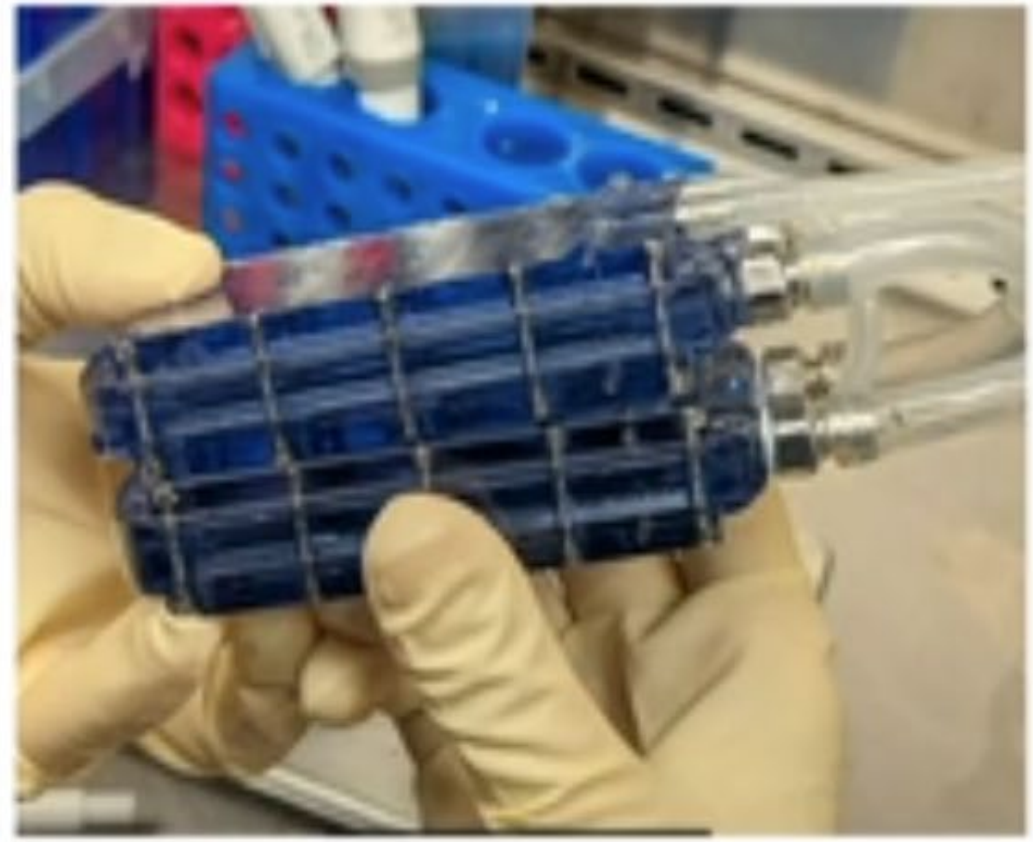
CJASN

Conclusions: Patients with kidney failure would trade risks of serious infection and death within 5 years for the benefit of complete mobility. These results will help inform manufacturers of next-generation implanted or wearable KRTs.

Leslie Wilson, Anne F. Gross, Lynda Frassetto, *et al.* ***Patient Preference Trade-Offs for Next-Generation Kidney Replacement Therapies.*** CJASN doi: 10.2215/CJN.0000000000000313. **Visual Abstract by Nayan Arora, MD**

Integrated Device - iBAK Prototype

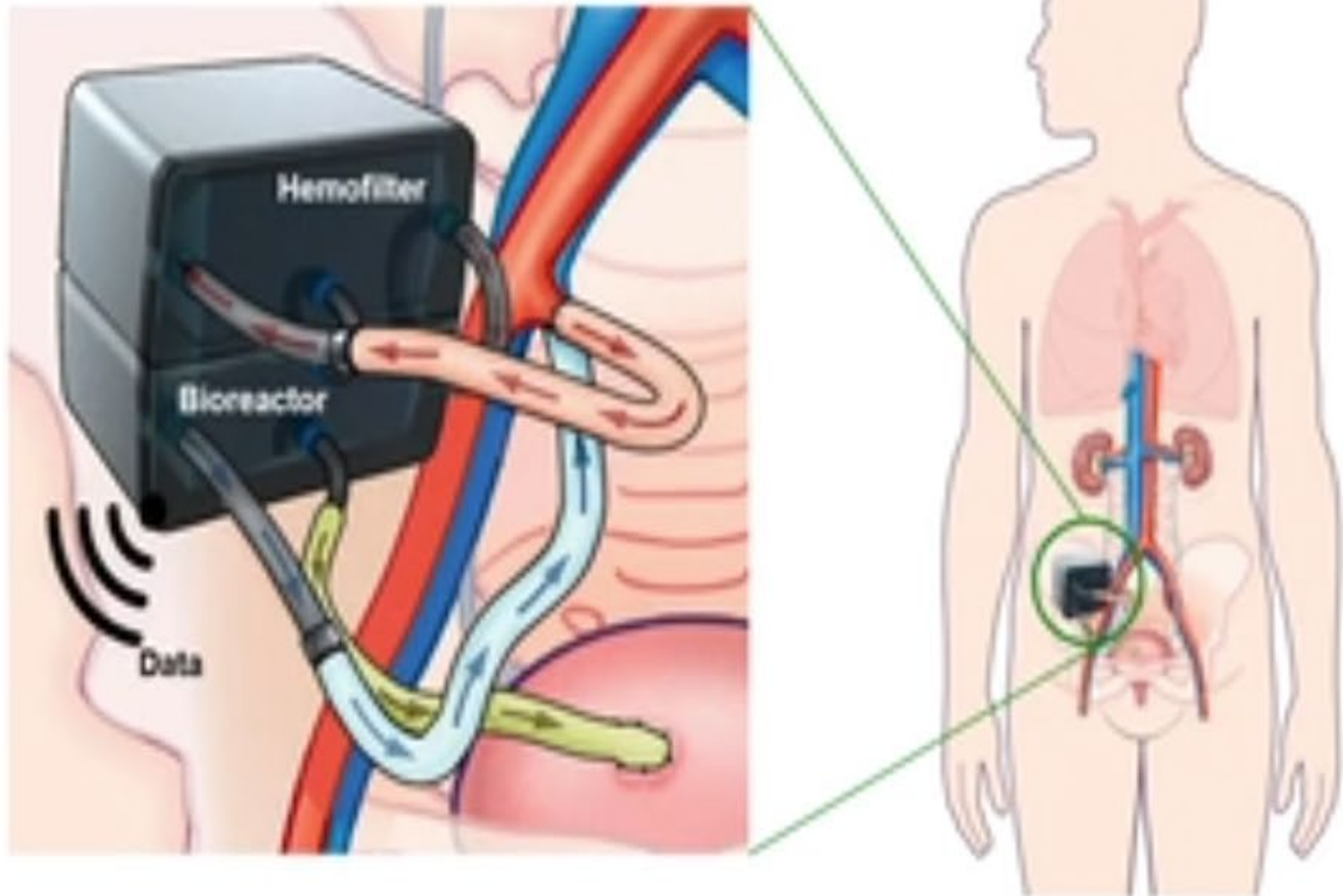




Chen et. al ASN Kidney Week 2021

Implantable Bioartificial Kidney (iBAK)

- Continuous treatment
- Freedom of mobility
- Decreased infection risk
- Physiological therapy
- No immunosuppression

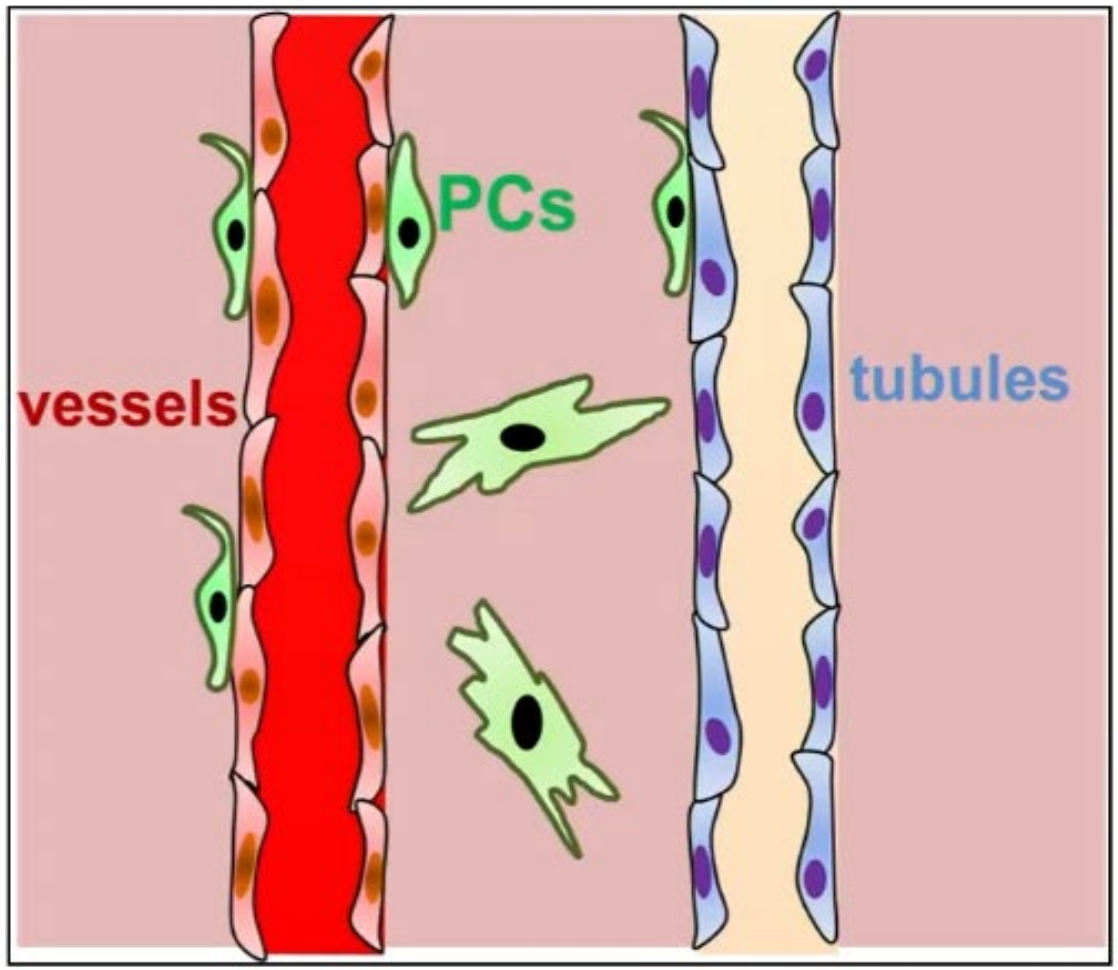


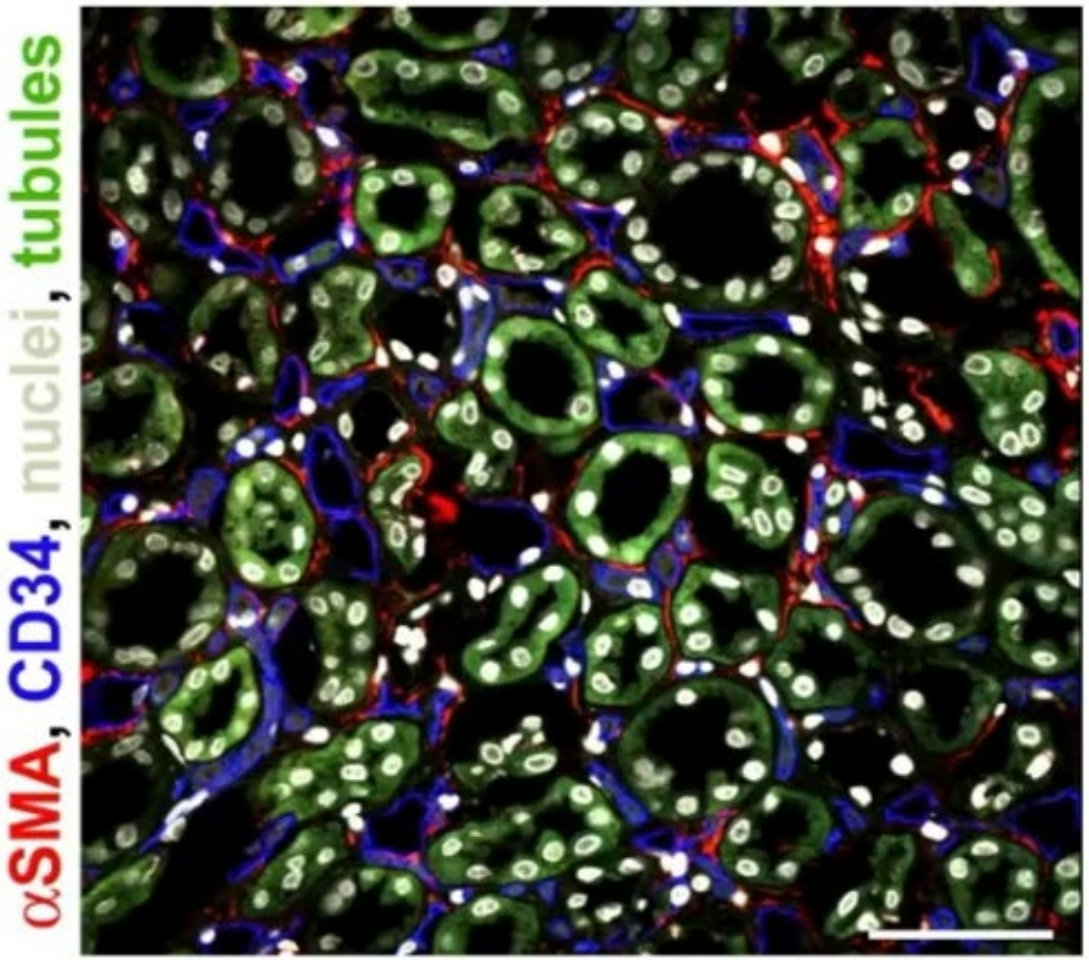
(Initial) Target Specifications = Design Input

- Package size of 500-750 ml → Anatomy
- Urea clearance of 20-30 ml/min → Hemofilter
- Fluid excretion of 2-3 liters/day → Urine
- Salt removal
  - Sodium: 100-200 mmol/day
  - Potassium: 100 mmol/day
  - Bicarbonate: 50-100 mmol/day

} Bioreactor

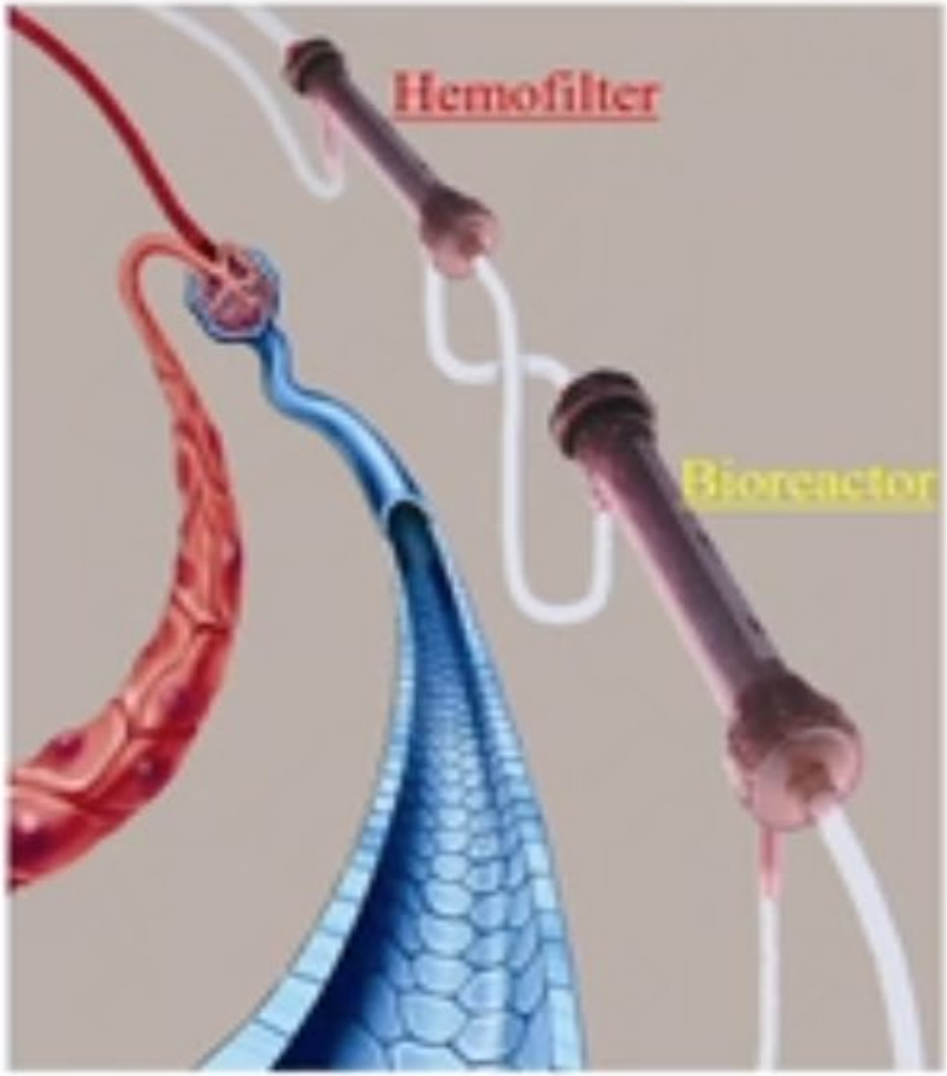
Isolation & purification of primary cells from human kidney





Pioneering Renal Cell Therapy

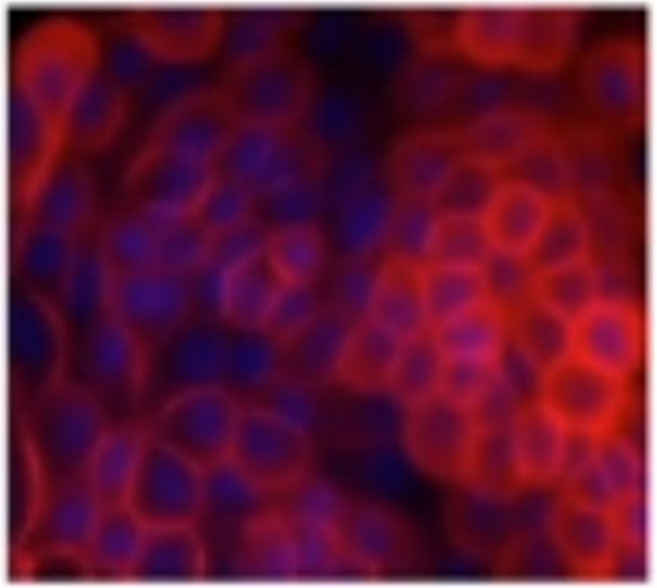
H. David Humes, MD
University of Michigan, USA



Biohybrid Strategy to Recapitulate Kidney Architecture

GLOMERULUS

BUILD
what we cannot
GROW PRECISELY

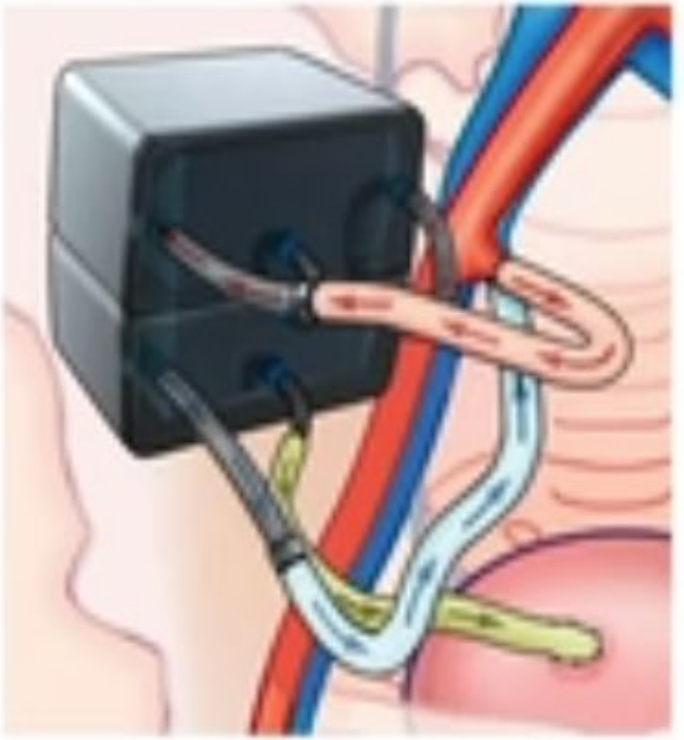


TUBULE

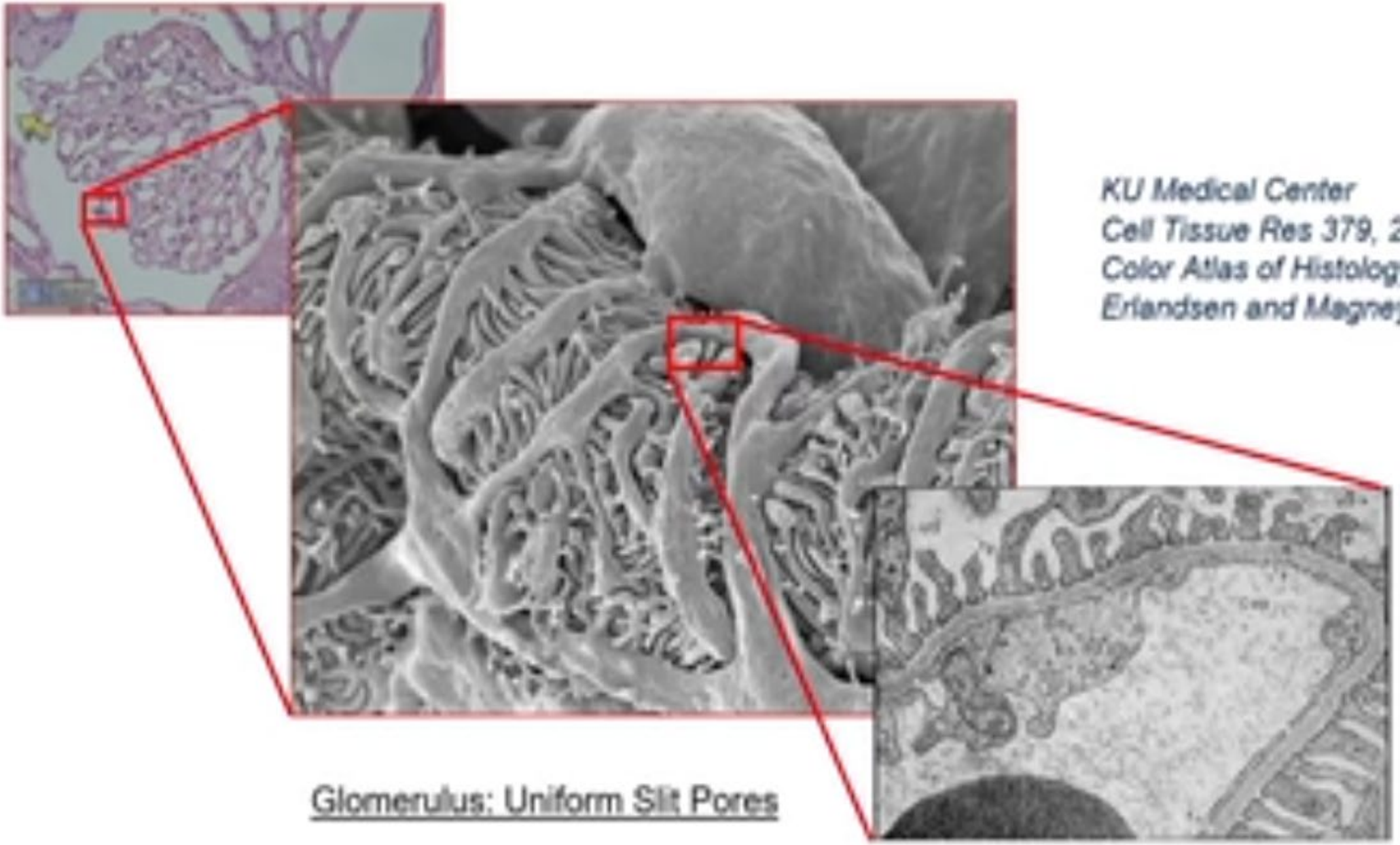
GROW
what we cannot
BUILD PRECISELY

Engineering a Biohybrid Device = Design Process

The Kidney Project



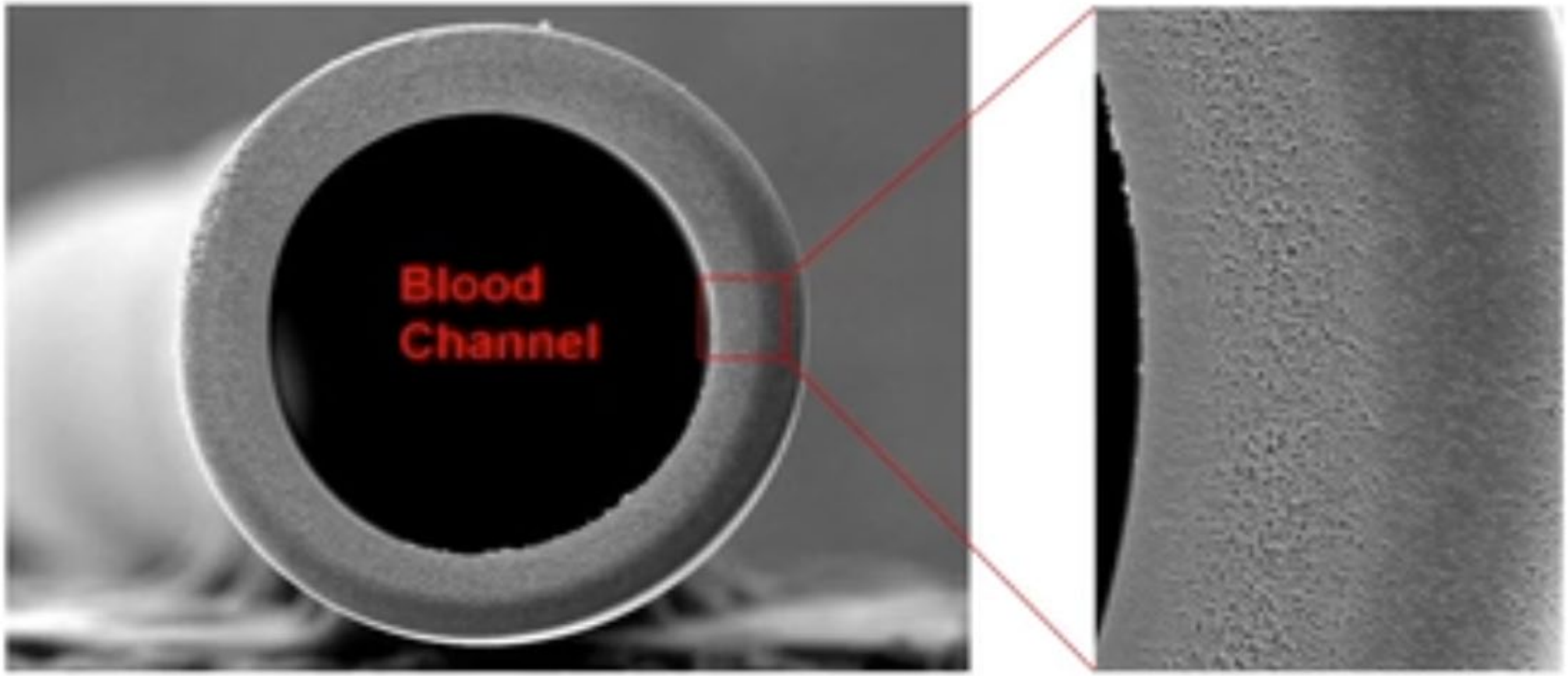
Natural Hemofilter



KU Medical Center
Cell Tissue Res 379, 245–254 (2020)
Color Atlas of Histology, 1992,
Erlandsen and Magney

Glomerulus: Uniform Slit Pores

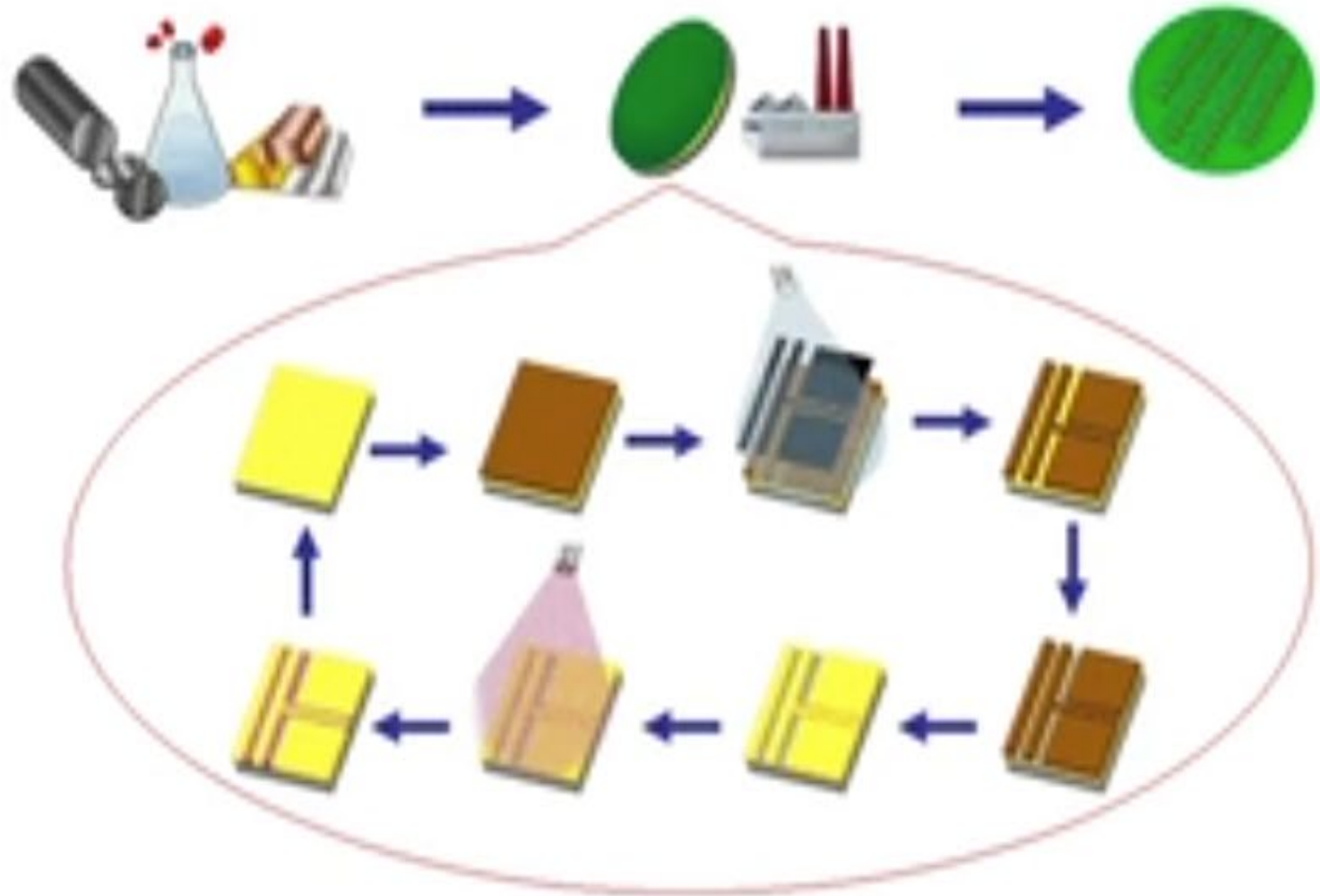
Artificial Hemofilter



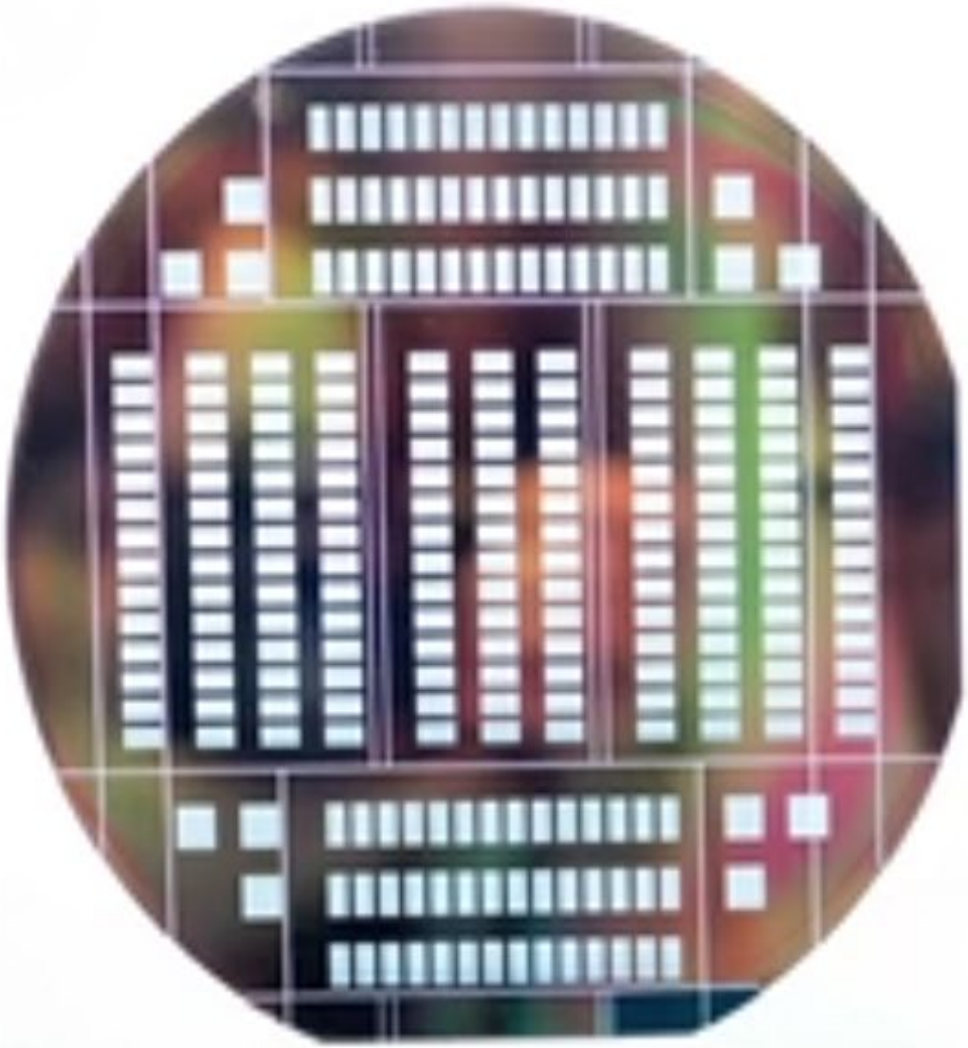
Porous Wall: Tortuous, Polydisperse Pores

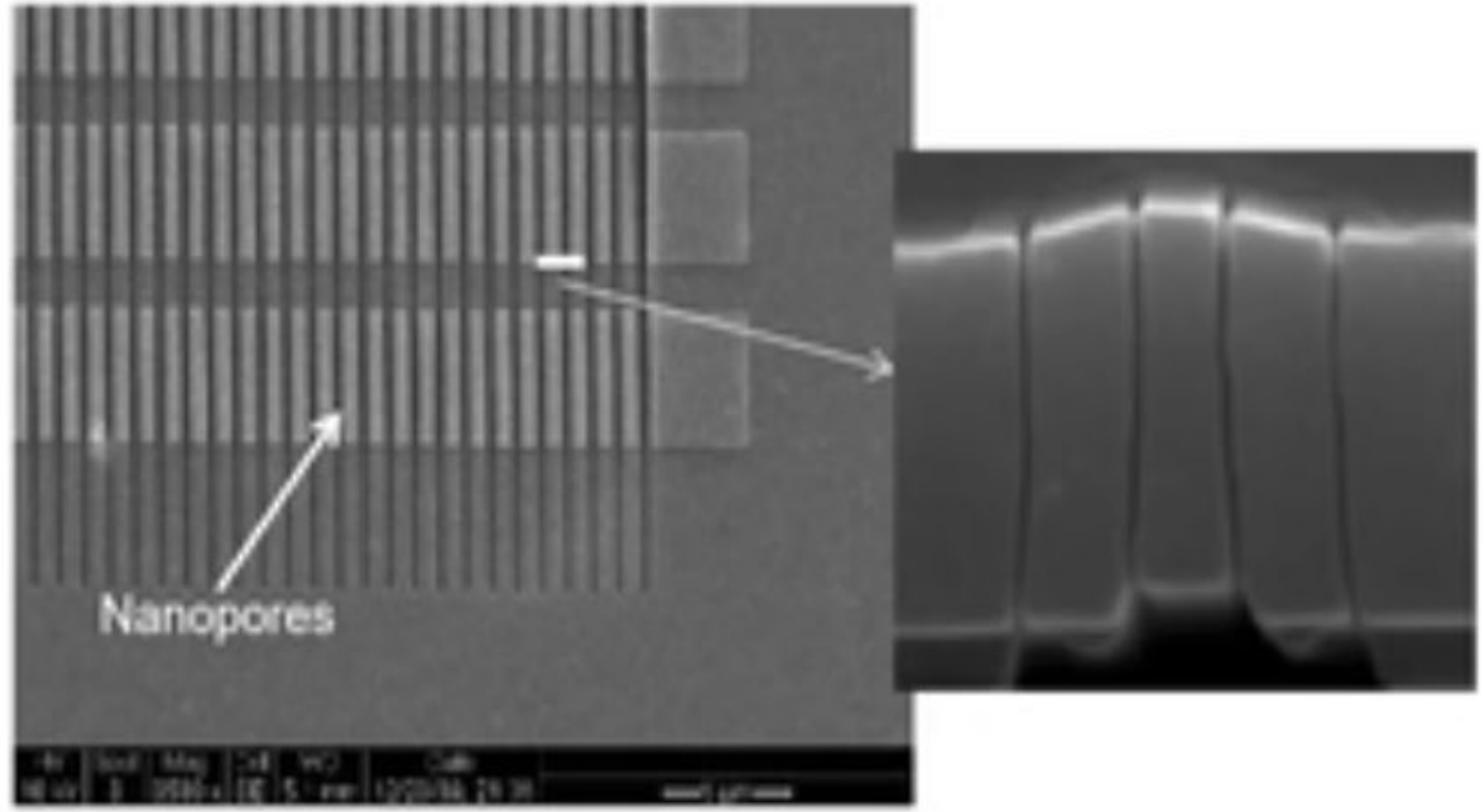
Repligen: Spectrum® mPES Hollow Fiber Filter Modules

Semiconductor Nanotechnology



Silicon Nanopore Membranes (SNM)

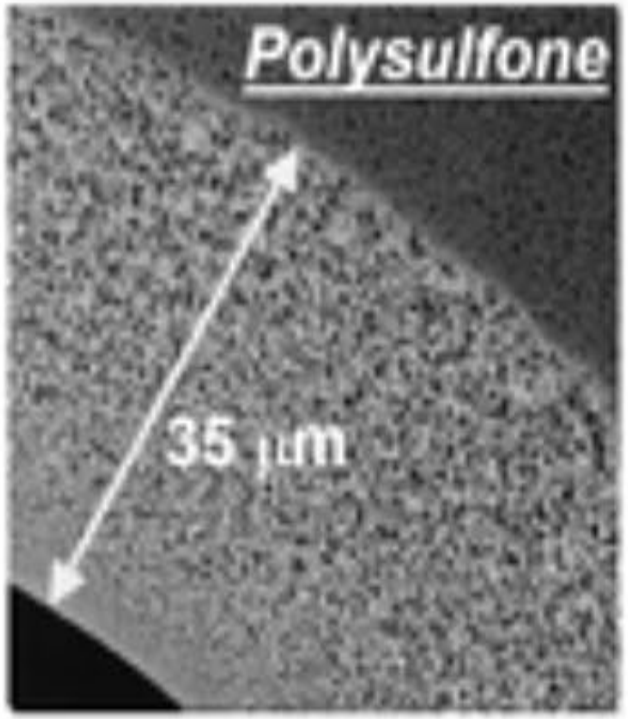


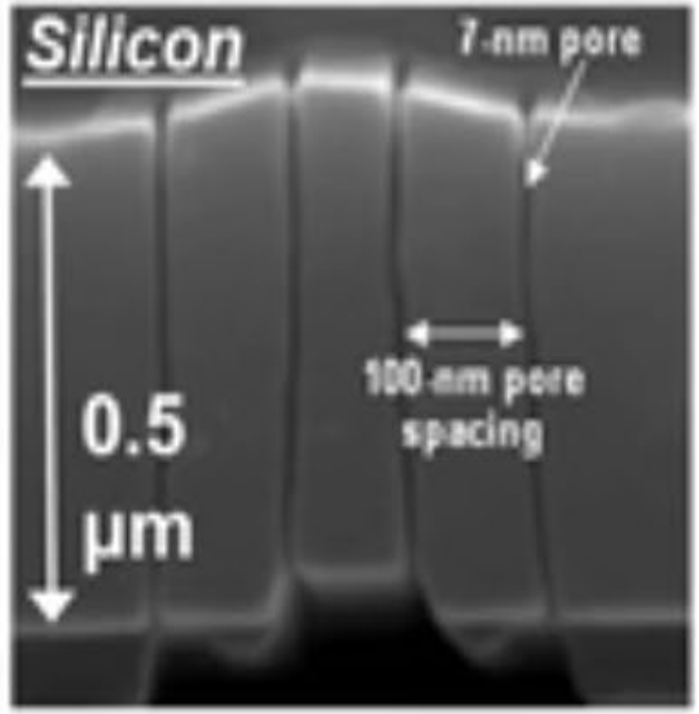


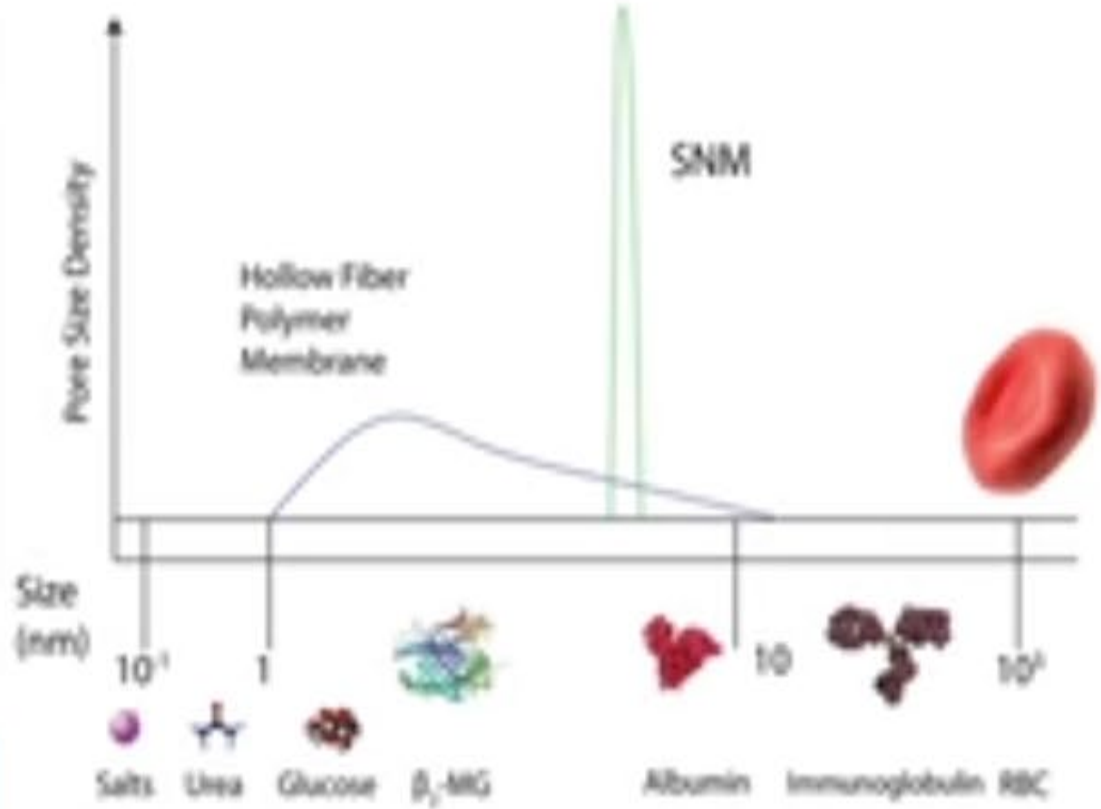
- High Molecular Selectivity
- Low Fluidic Resistance
- Batch Manufacturing

Biodesign Laboratory, UCSF

SNM vs Hollow Fiber Membrane







	SNM	Polysulfone (Optiflux F160NR)
Hydraulic Permeability (ml/hr/mmHg/m^2)	200-600	10-30

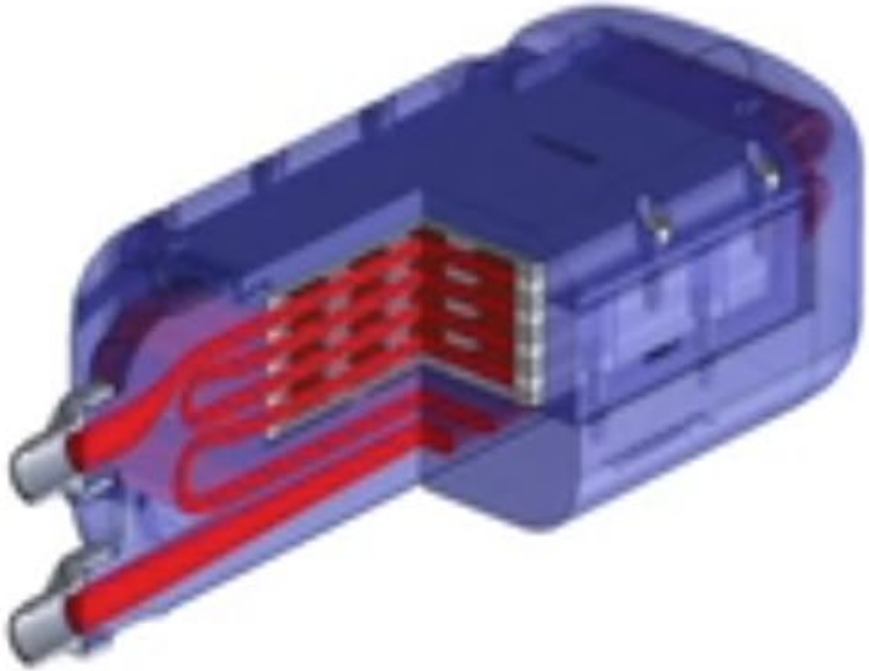
No Pumps

Improved Clearance

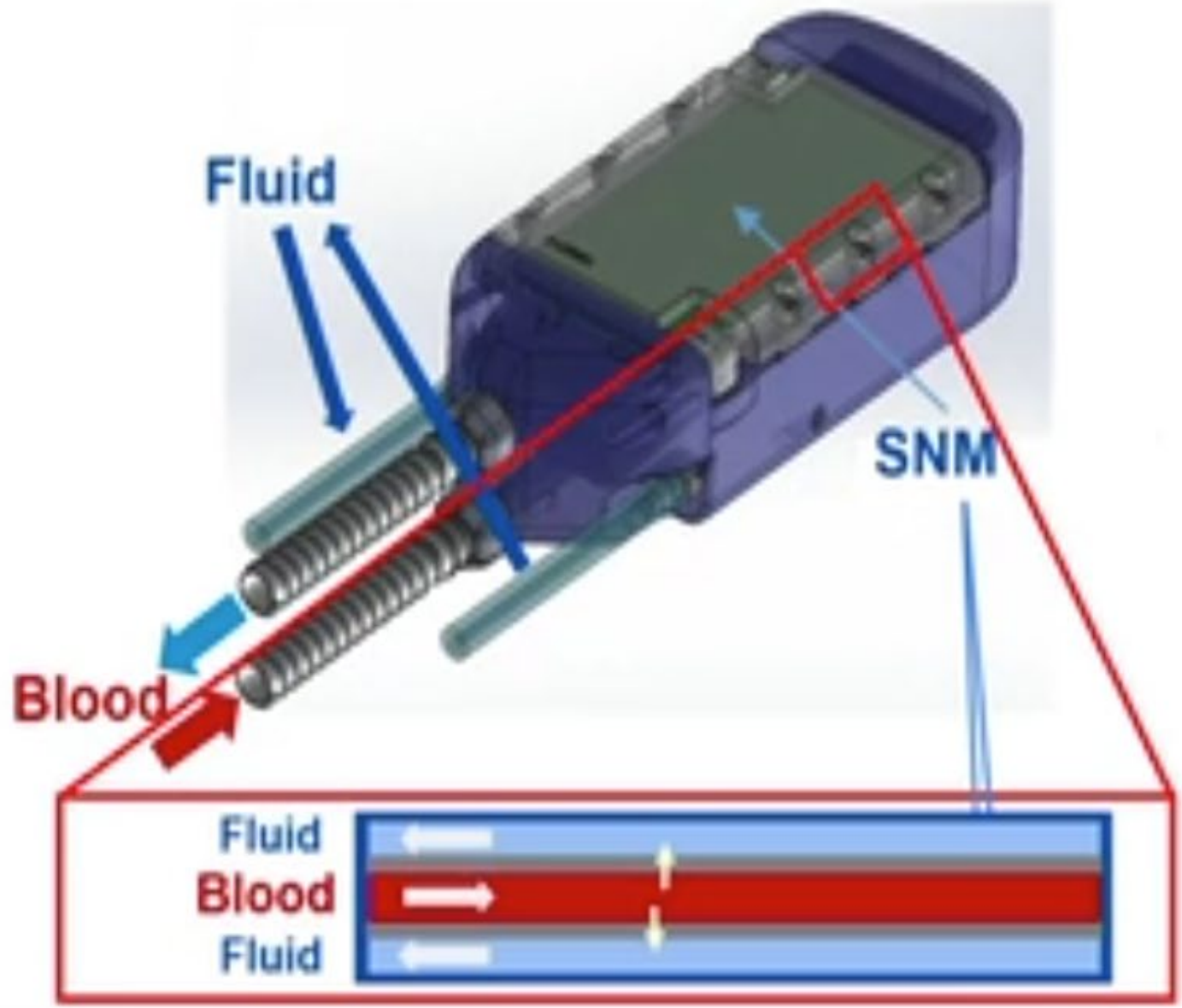
Biodesign Laboratory, UCSF
https://www.mdpi.com/2077-0375/11/10/767

SNM Hemofilter: Device Refinement

- Parallel SNM configuration
  - Low blood flow resistance
  - Eliminates blood pumps
  - Perfusion-pressure blood flow

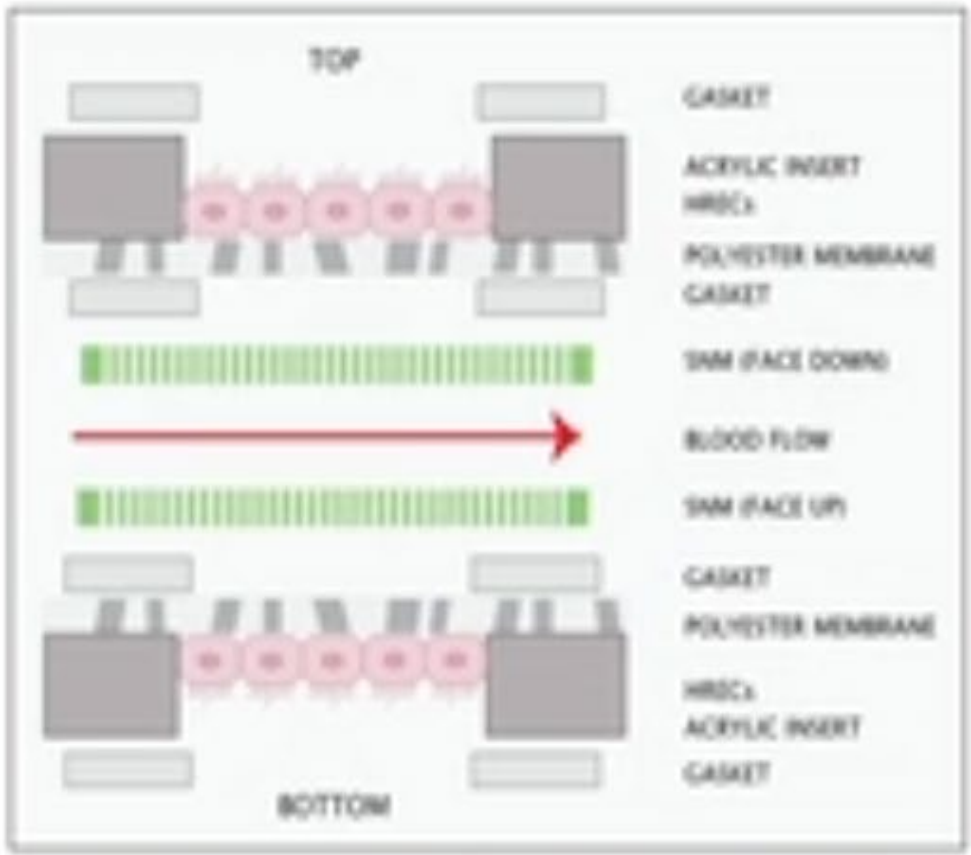


Moyer et. al ASN Kidney Week 2018

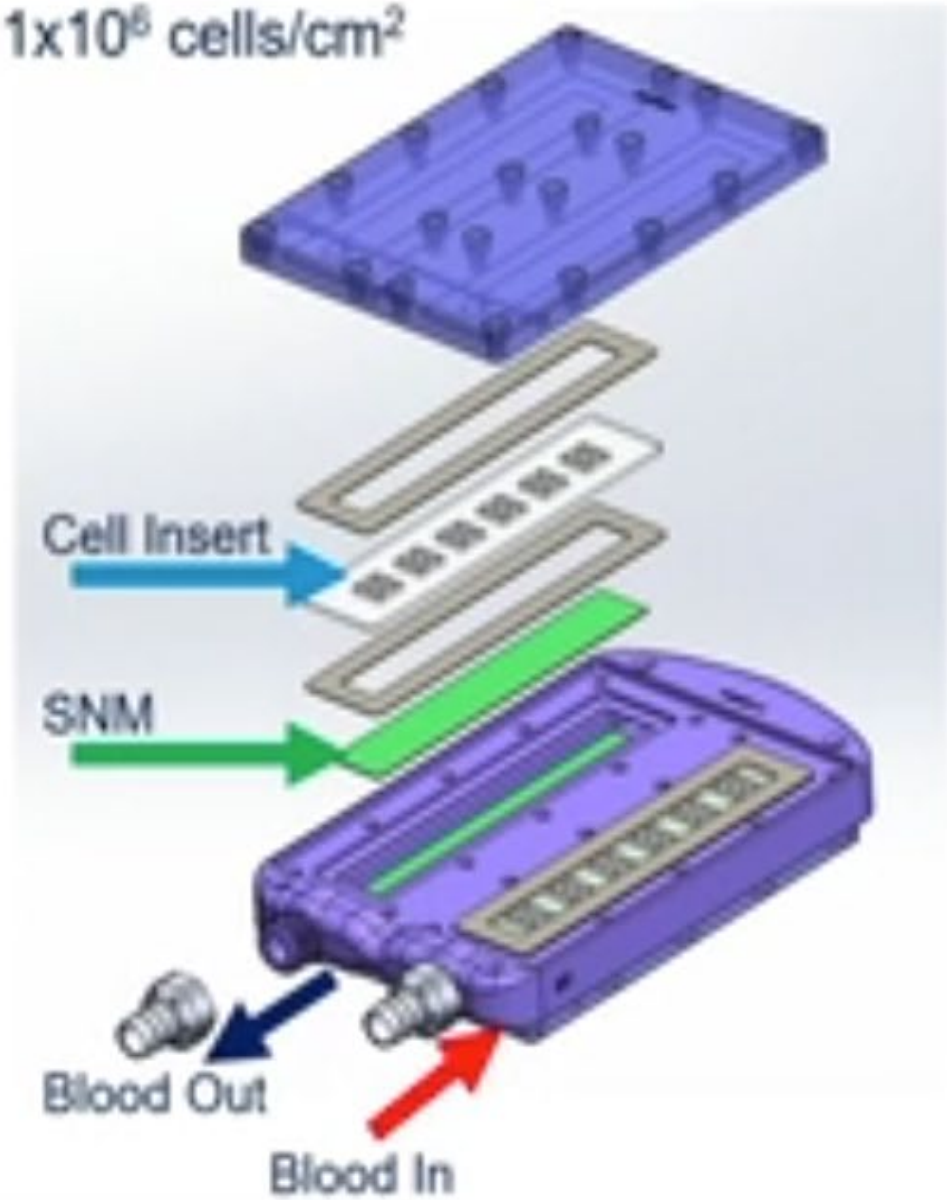


SNM Bioreactor: Device Construction

- Analogous to hemofilter
  - SNM for immunoprotection
  - Primary human renal tubule cells

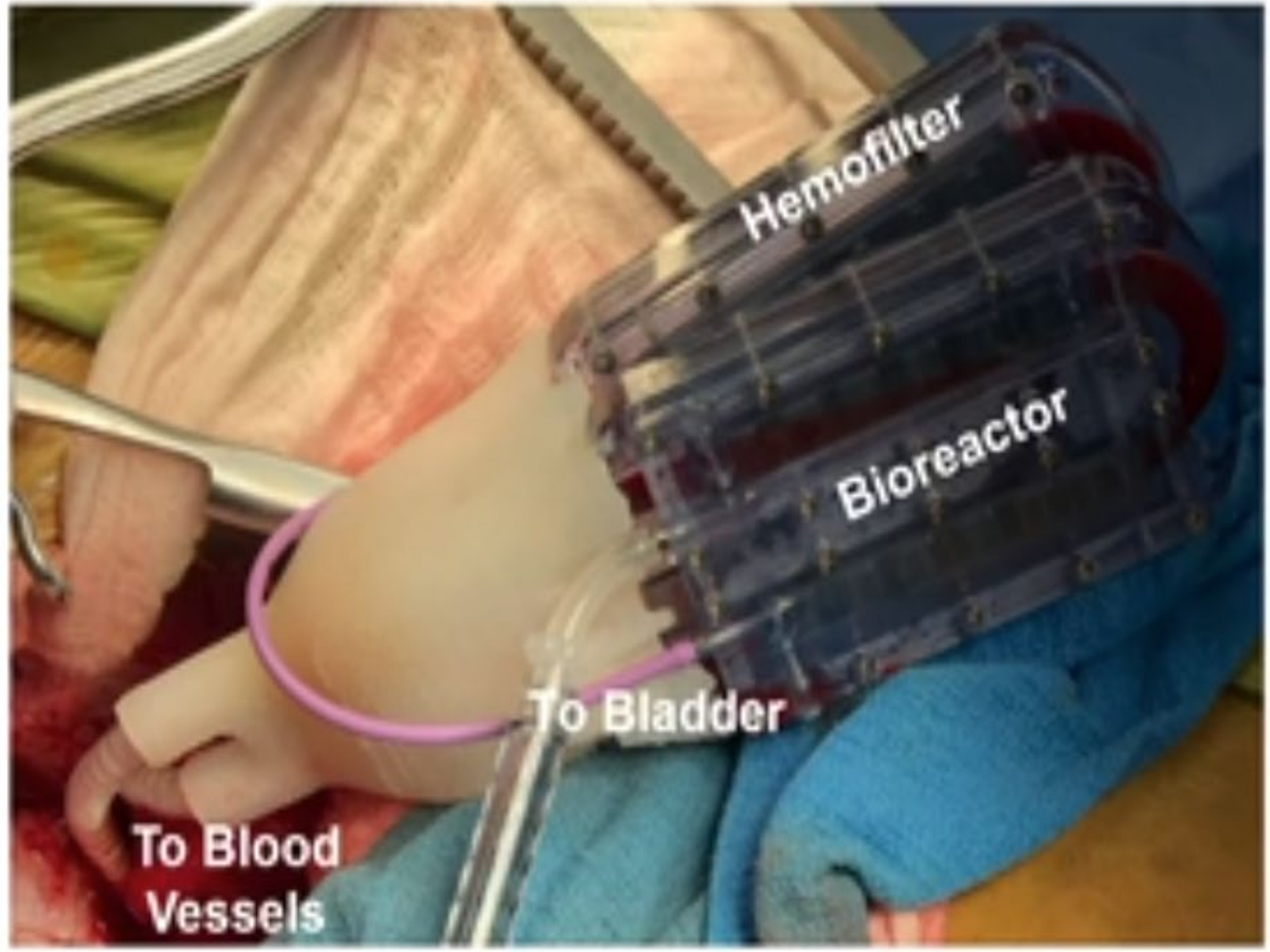


1x10^6 cells/cm^2



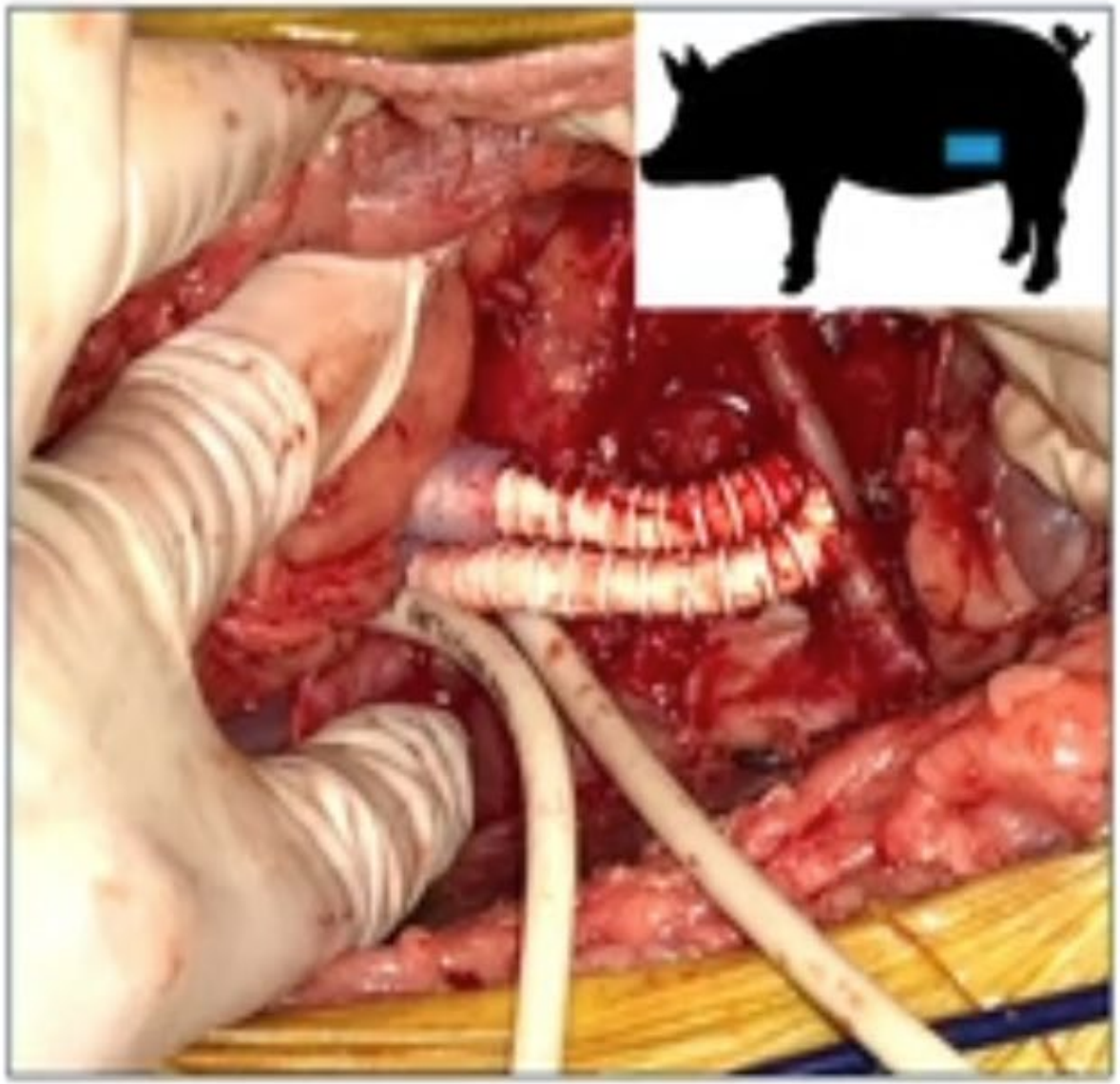
Gologorsky et. al ASN Kidney Week 2019 (Washington, DC)

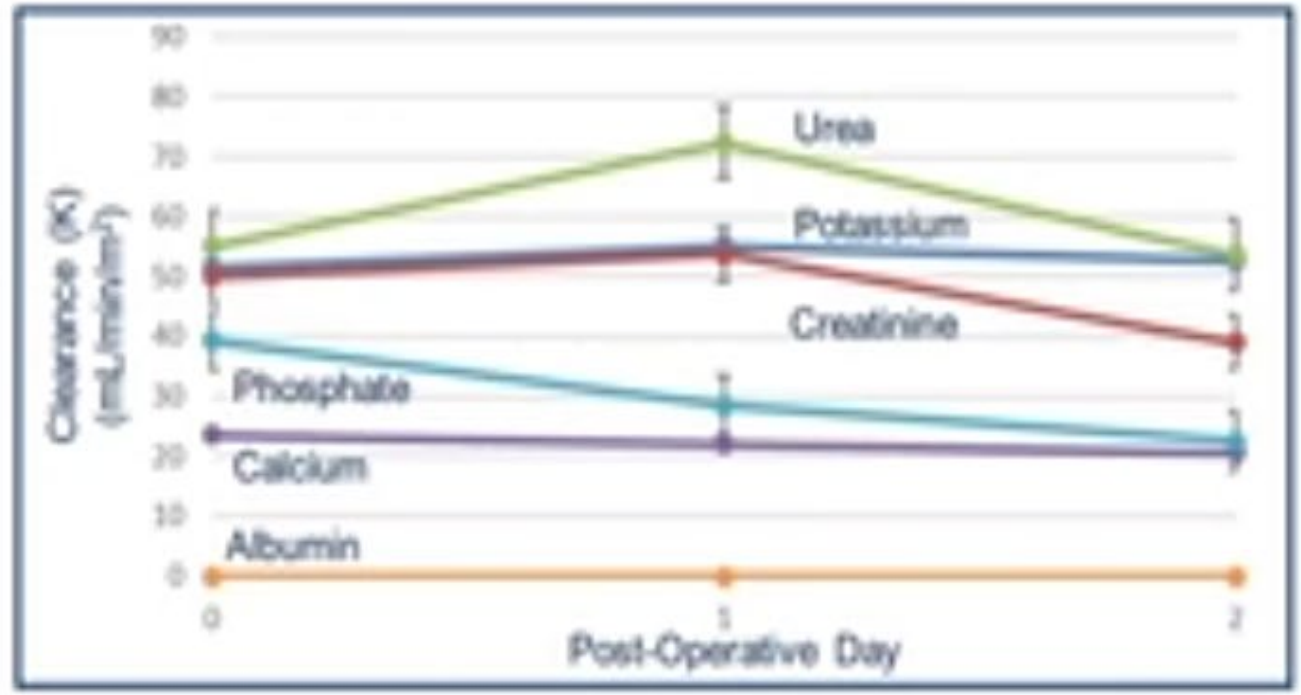
Device Implantation



SNM Hemofilter: 3 Day Implantation

Moyer et. al ASN Kidney Week 2018

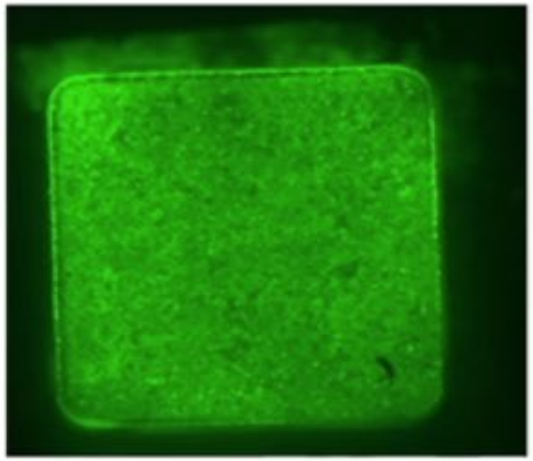




Device Performance – 3 Day Implantation

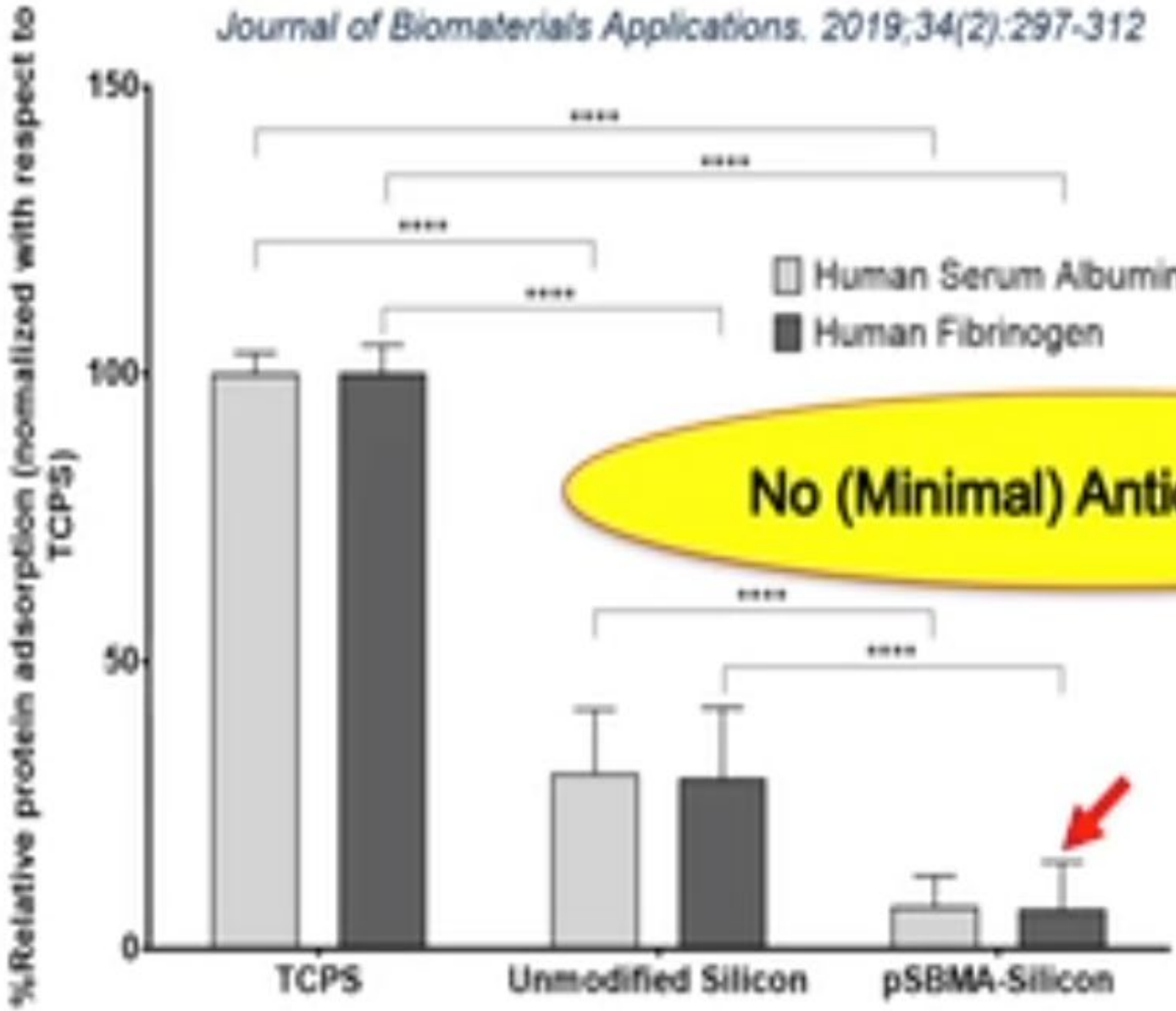
- 5 nm SNM and LLC-PK1 cells
- Hemofilter output: 4 ul/min
- Bioreactor reabsorption: 93%
- Cell viability: 95%

Chen et. al ASN Kidney Week 2021



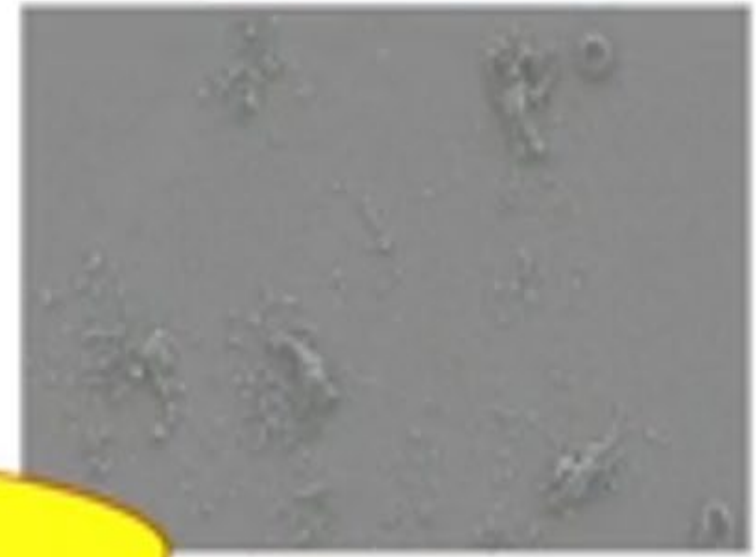
Biocompatible Coatings

Journal of Biomaterials Applications. 2019;34(2):297-312



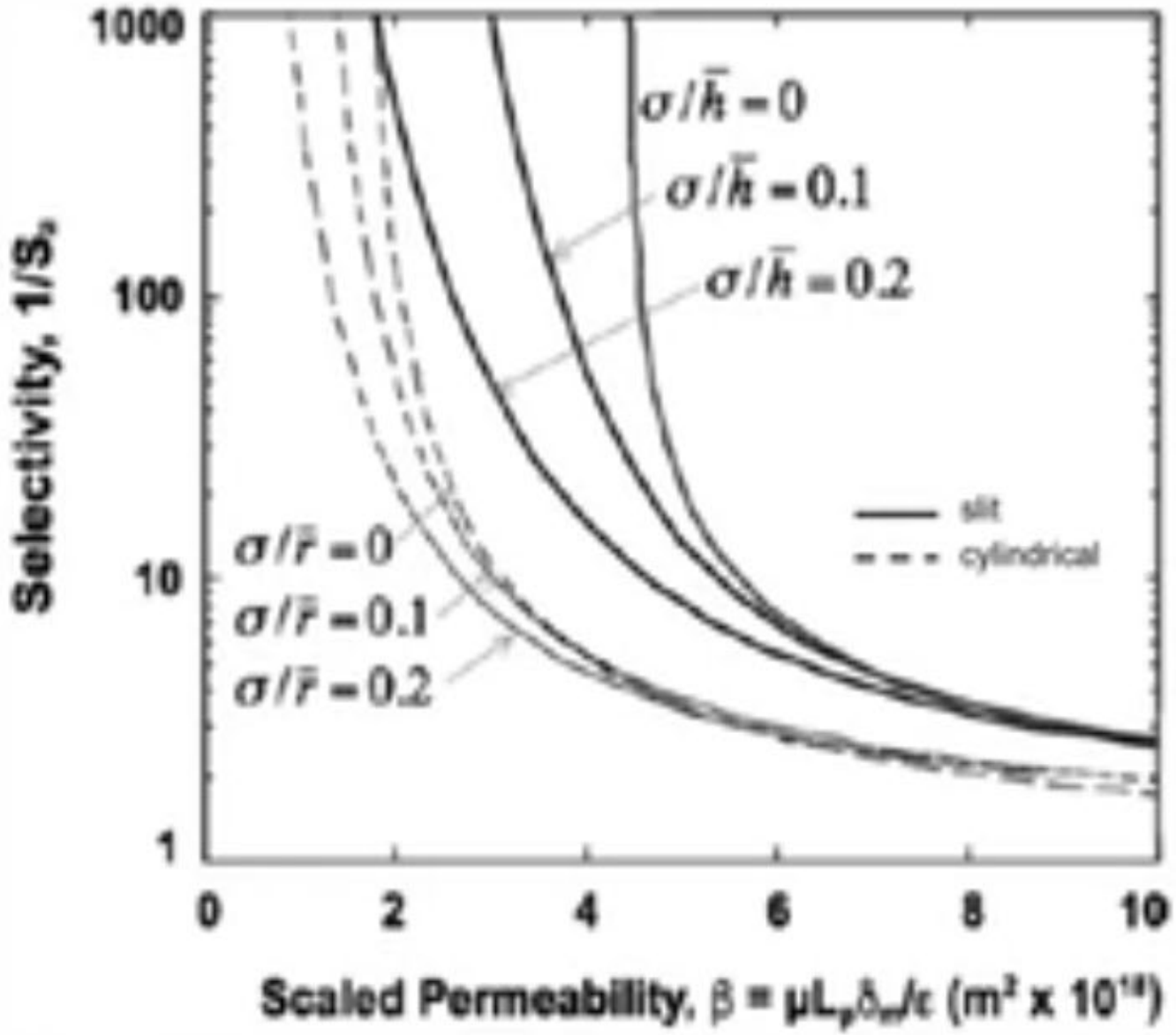
No (Minimal) Anticoagulation

Unmodified Silicon



pSBMA-Silicon

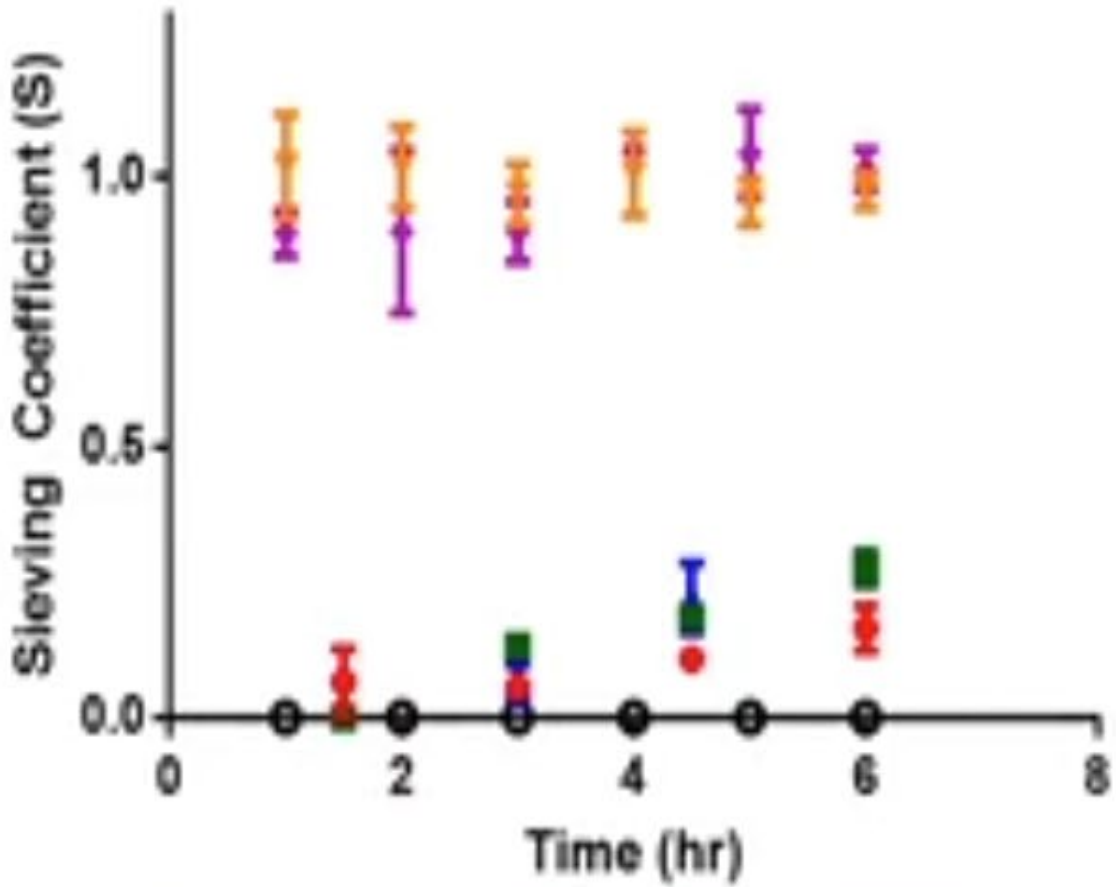
Filtration Efficiency: Slit vs Cylindrical Pore



Slit >> Cylindrical

J Memb Sci. 2010 Mar 1; 349(1-2): 405

SNM Selectivity



No (Minimal) Immunosuppression

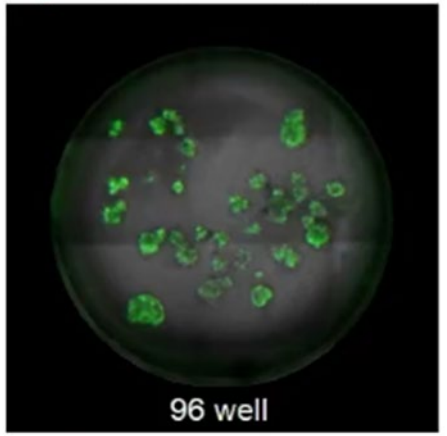
- 80% reduction in cytokine passage
- 100% passage of glucose and insulin
- No passage of albumin or antibodies

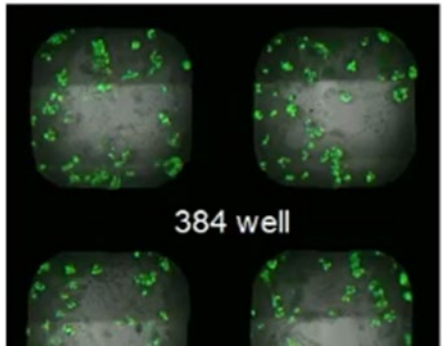
Sci Rep 6, 23679 (2016)

What is a 'kidney organoid'?

"A multicellular unit *in vitro* containing nephron-like epithelial structures with podocyte and tubular segments"

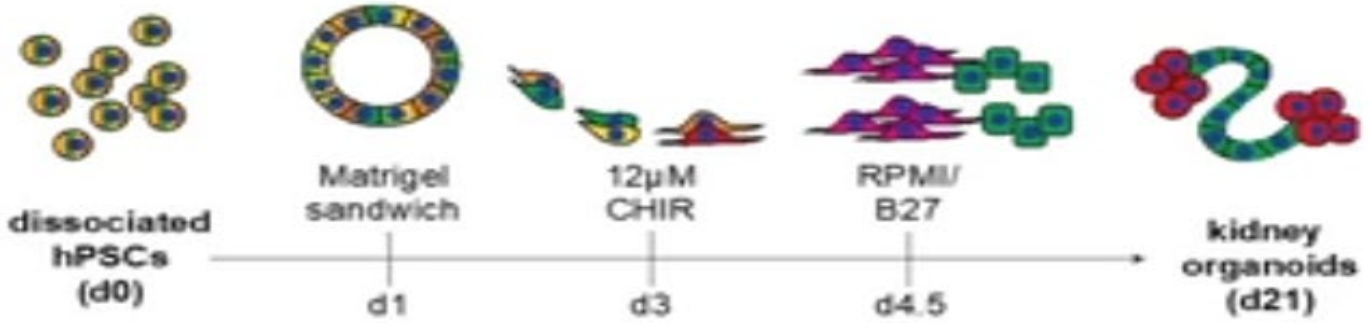
proximal tubule/phase



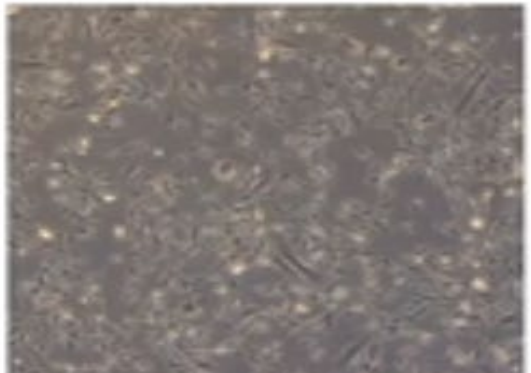


Creating human stem cells and organoids from urine samples for personalized medicine

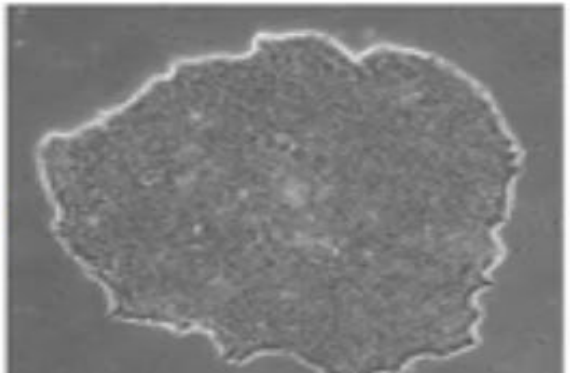
We have been able to isolate somatic cells from urine and/or blood from patients with kidney diseases and turn these cells into stem cells.



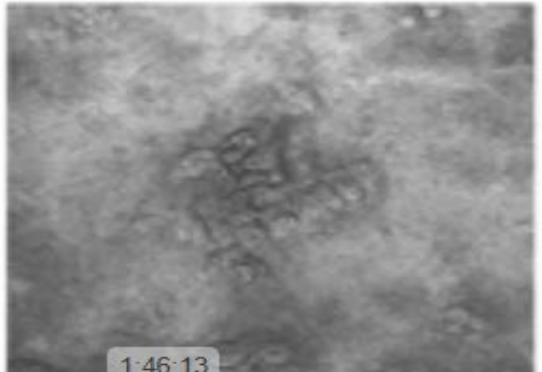
Urine derived cells



Induced pluripotent stem cells



Kidney organoid



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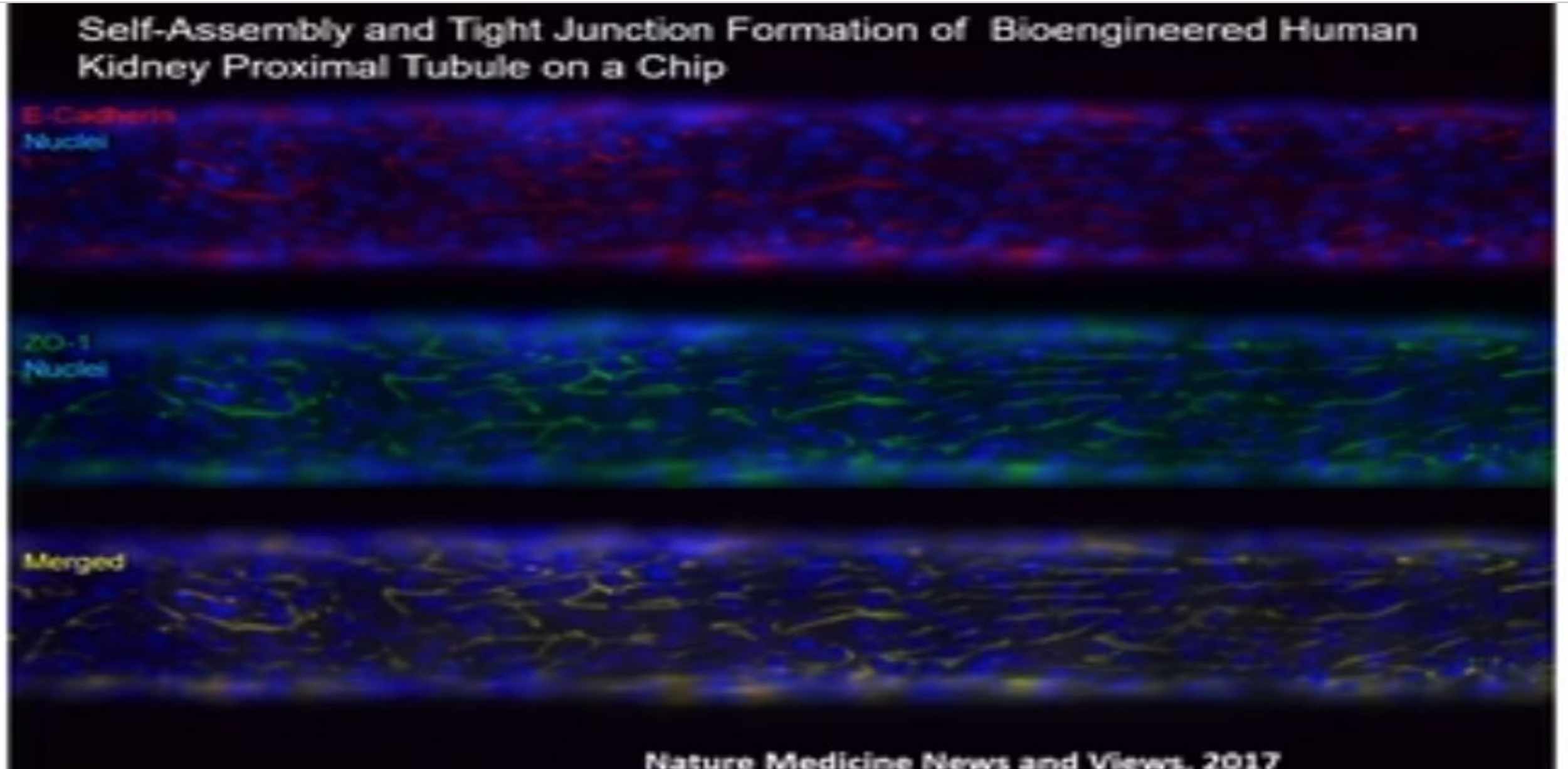
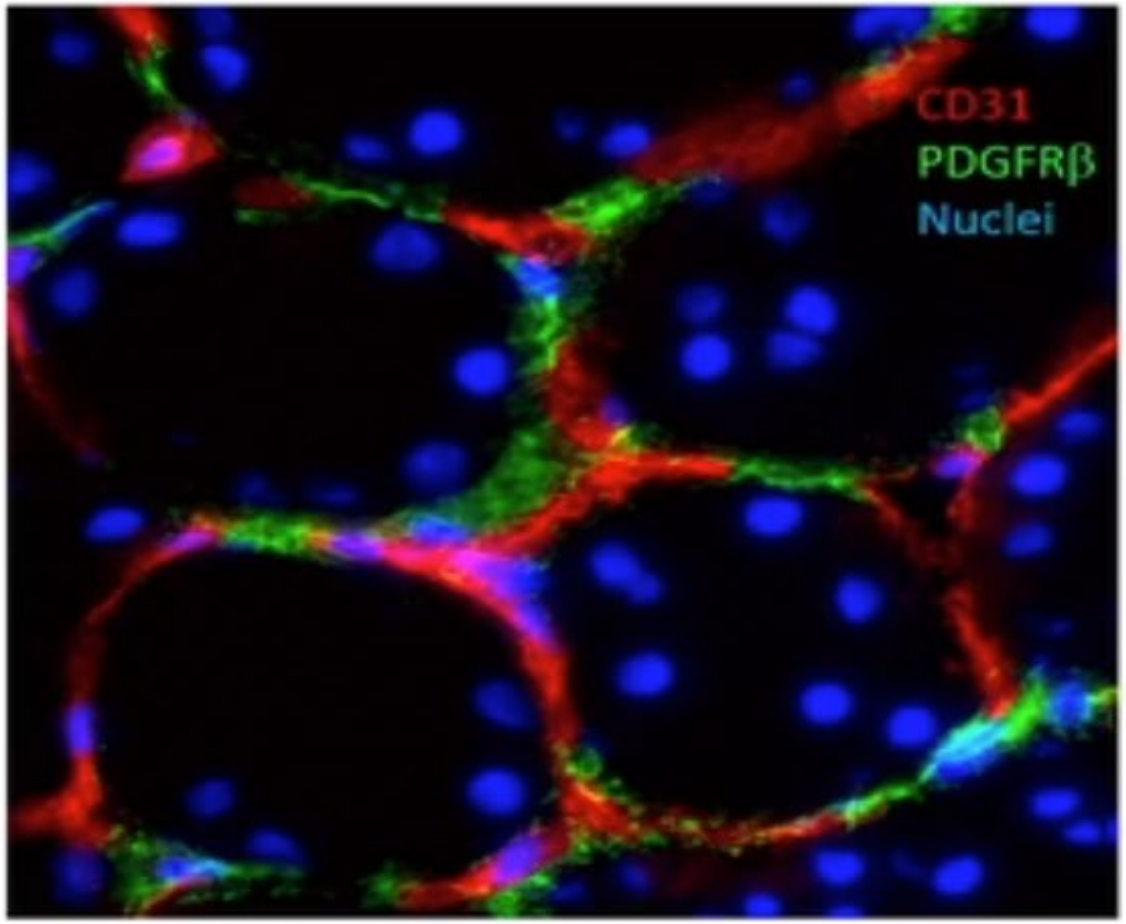
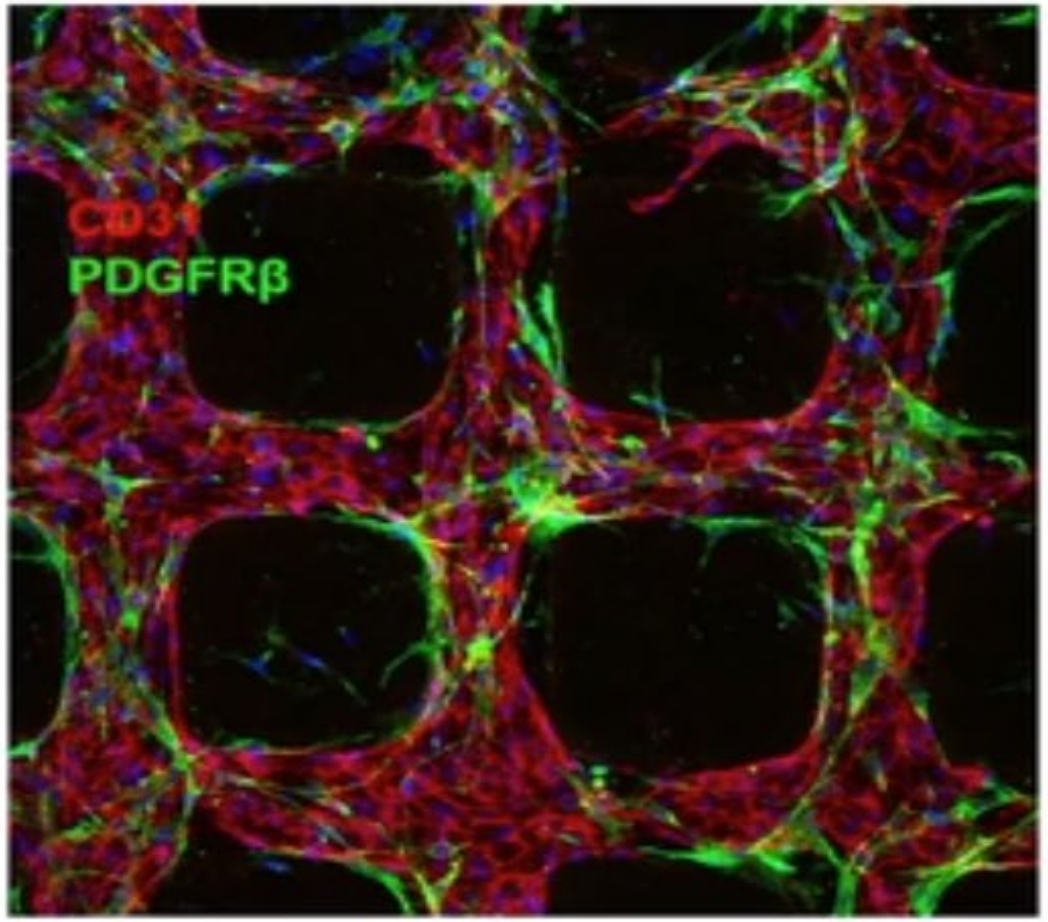


Bioengineered human kidney peritubular microvascular network

Ligresti et al, JASN, 2015





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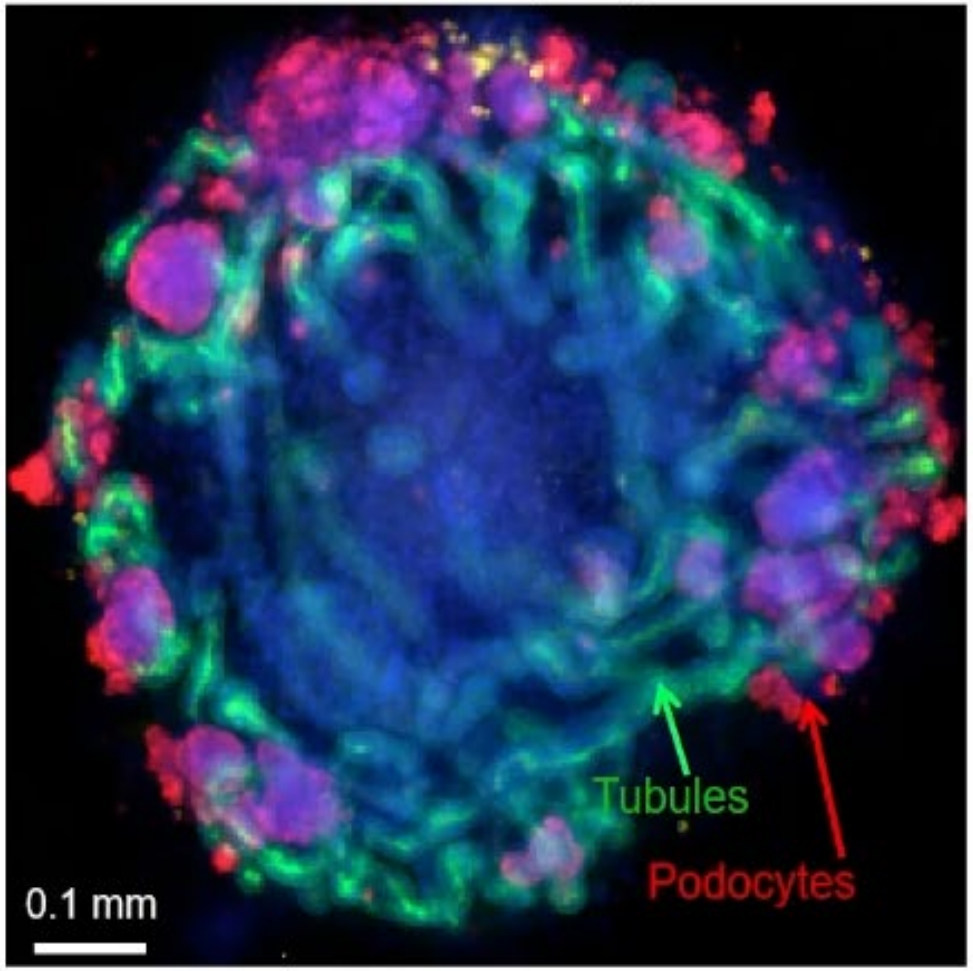
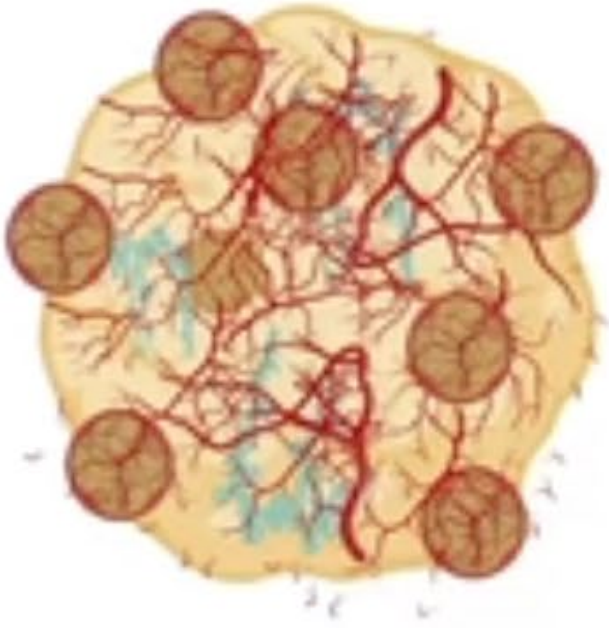
Human Kidney

Human Kidney Organoid



Freedman et al. *Nature Communi*[illegible]*ons*. 2015

The importance of vascularized kidney models



- ***Disease modeling***
- ***Pathway ID***
- ***Therapeutic development***
- ***High throughput compound testing***
- ***Transplant***

Ideal System

- Orthogonal differentiation
- Adaptable for suspension culture + other systems
- Applicable to other organs
- Reproducible
- Applicable for high throughput organoid generation
- Readily usable in injury models

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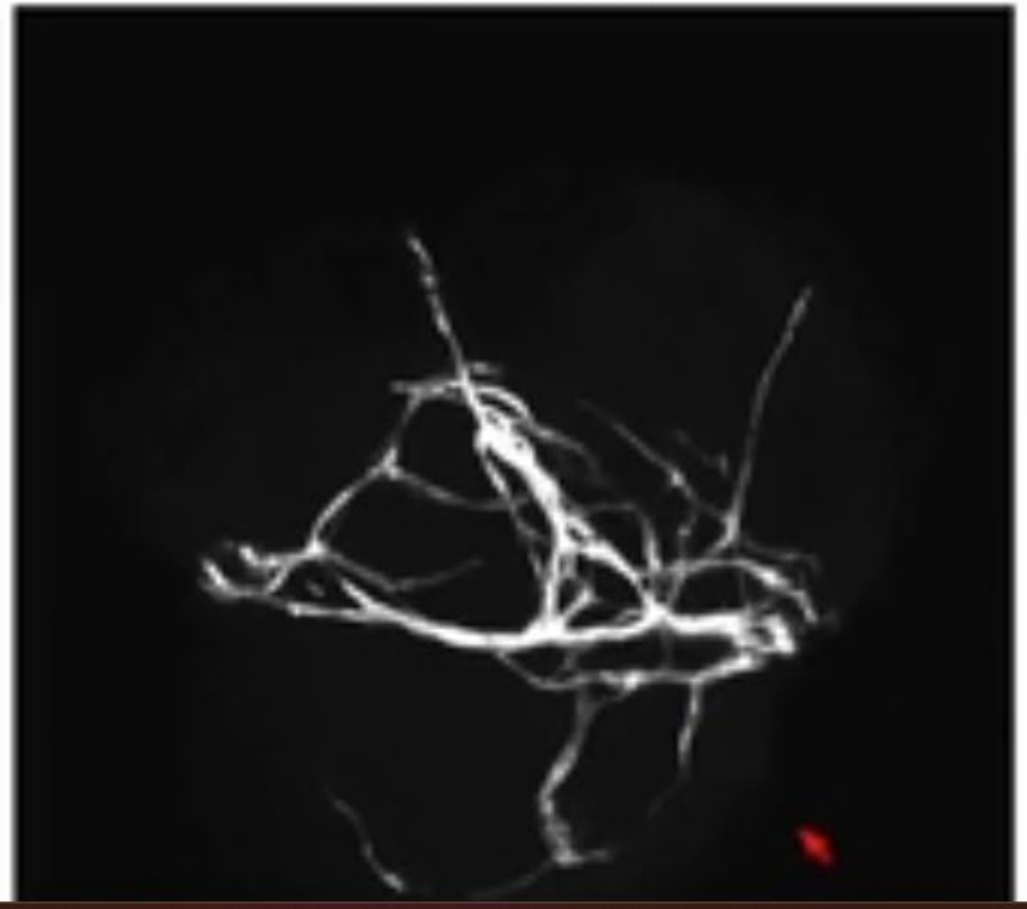
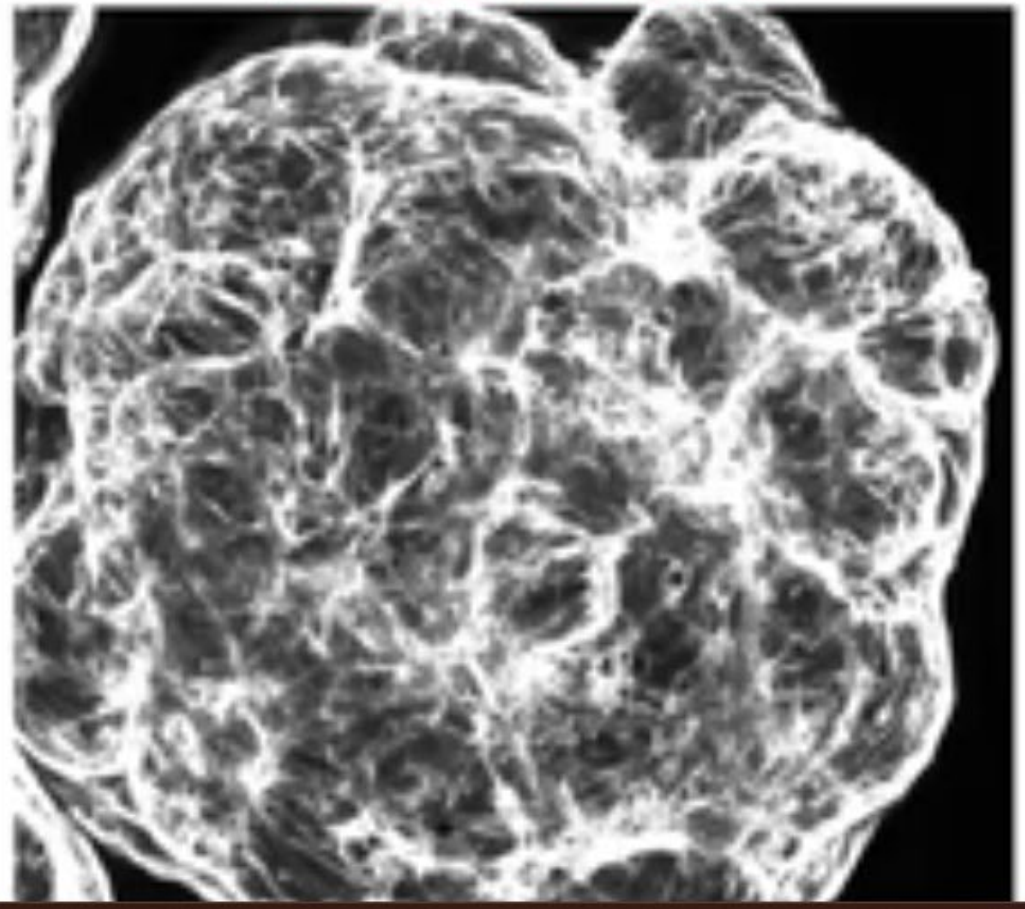
Endothelializing kidney organoids

Control



Vascularized



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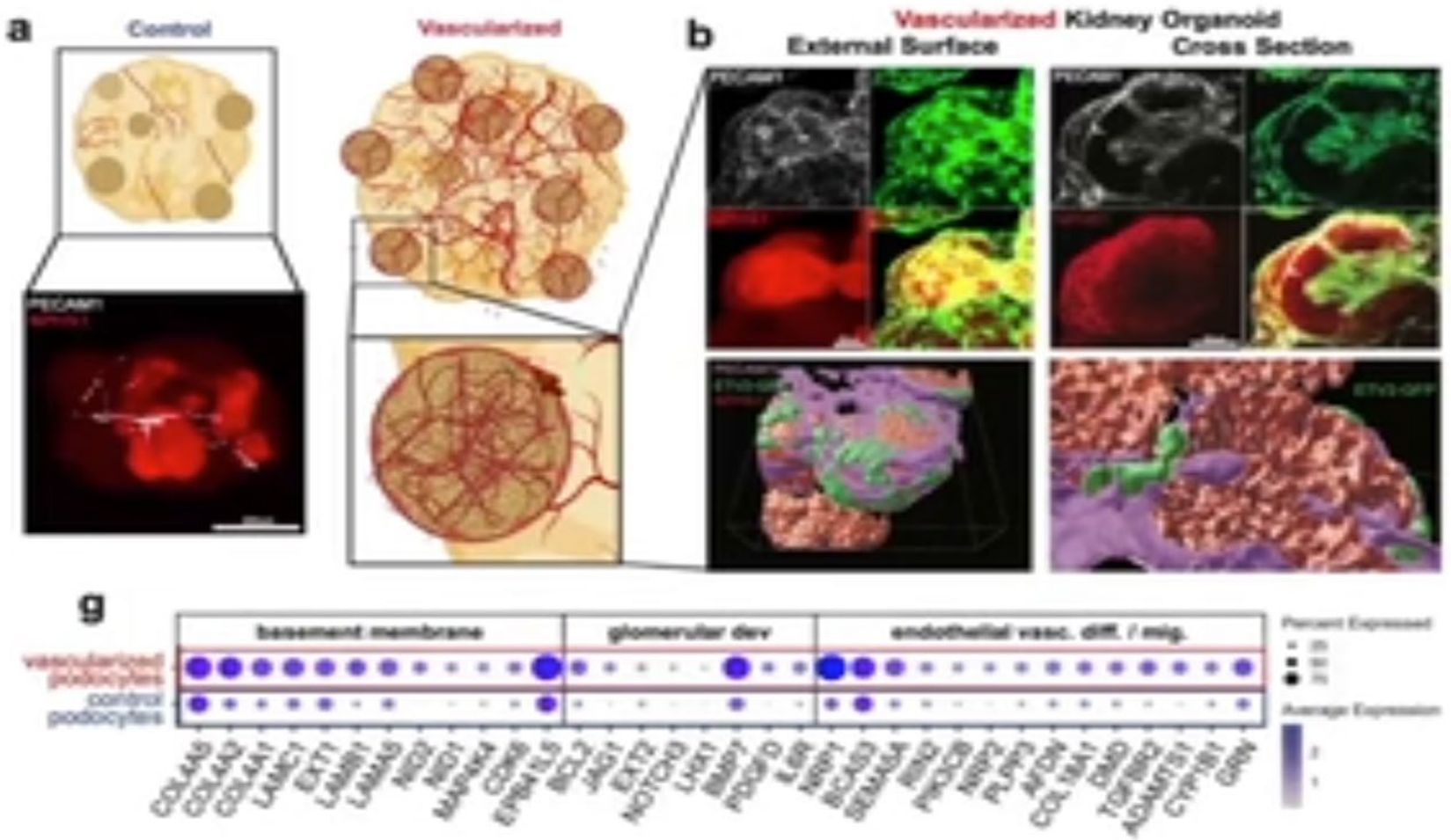
Endothelialization enables glomerulus-like formation



Maggiore, et. al., 2023, Submitted

SHATTUCK LECTURE

Innovation, Regulation, and the FDA

Margaret A. Hamburg, M.D.

"We are failing, as a scientific community and as a nation, to adequately deliver the promise of science to diagnose, treat, prevent, or cure disease... **We must invest in new methods, assays, standards, and models that will help speed the development, review, and approval of medical products that patients need and can rely on."**

NEJM, 2010

ARTIFICIAL KIDNEY :

A Light at the End of the Dialysis Tunnel