Progress Towards An Implantable Artificial Kidney

MEPTEC 9th Annual MEMS Symposium

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Background on Kidney Disease

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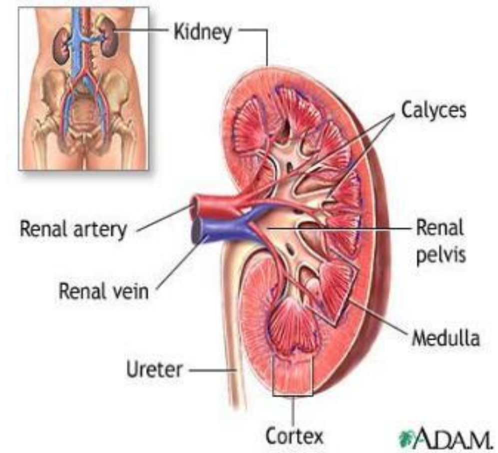
- **Key functions of kidneys**
  - removal of wastes
  - regulate electrolytes
  - maintain acid-base balance
  - regulate blood pressure
  - secrete hormones



- **Chronic kidney disease (CKD)**
  - slow, progressive loss of function
  - affects over 25 million Americans
  - graded in stages: Stage I, II, III, IV, V
  - Stage V is end stage renal disease (ESRD)
    - kidney failure

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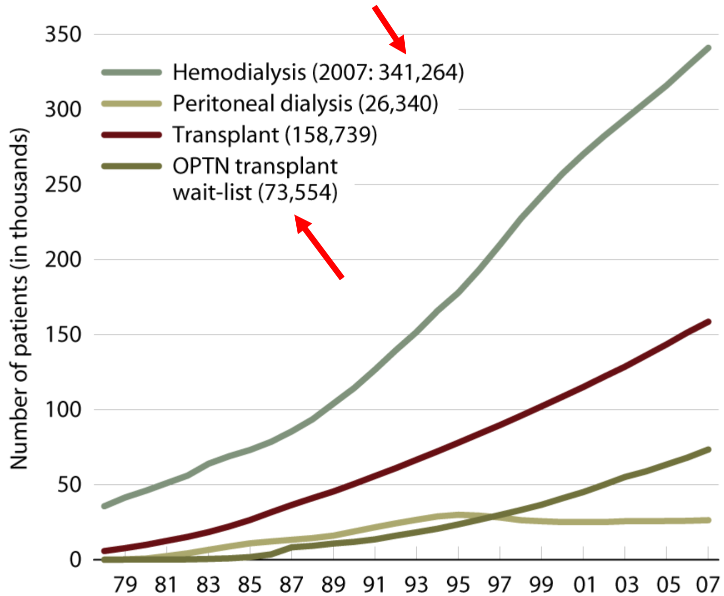
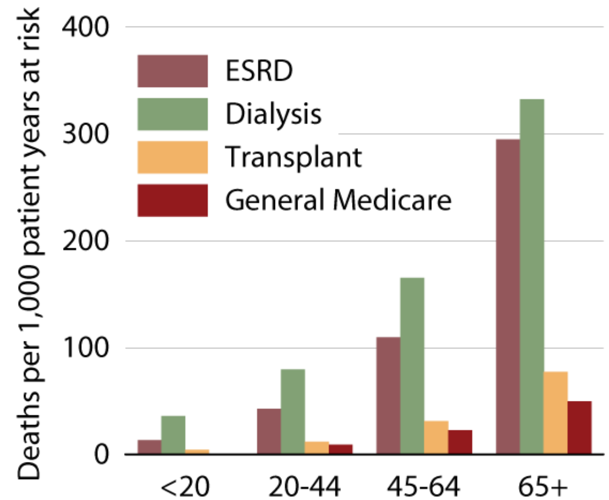
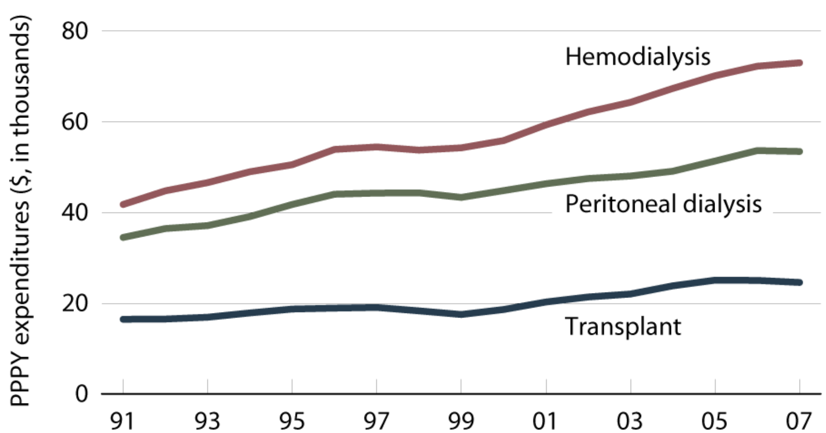
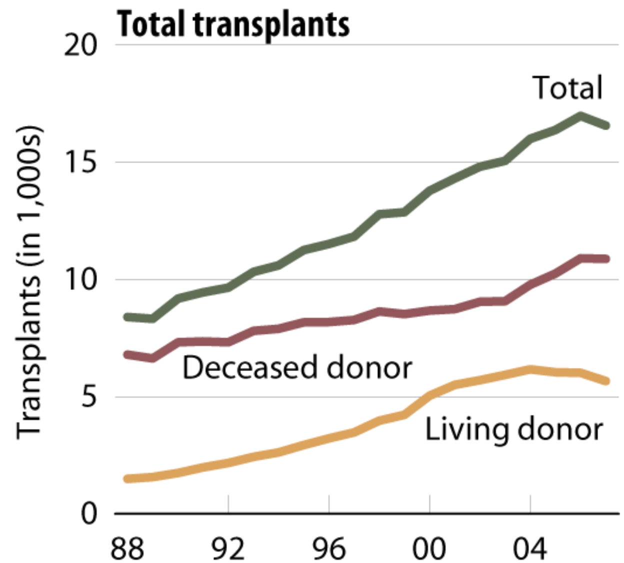
USRDS 2009 ESRD Statistics









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Biomimetic Device

- **Dialysate-free**
  - convective filtration
  - selective reabsorption
- **2 primary components**
  - hemofilter
    - toxin clearance
  - cell bioreactor
    - volume homeostasis
    - metabolic function
    - electrolyte balance

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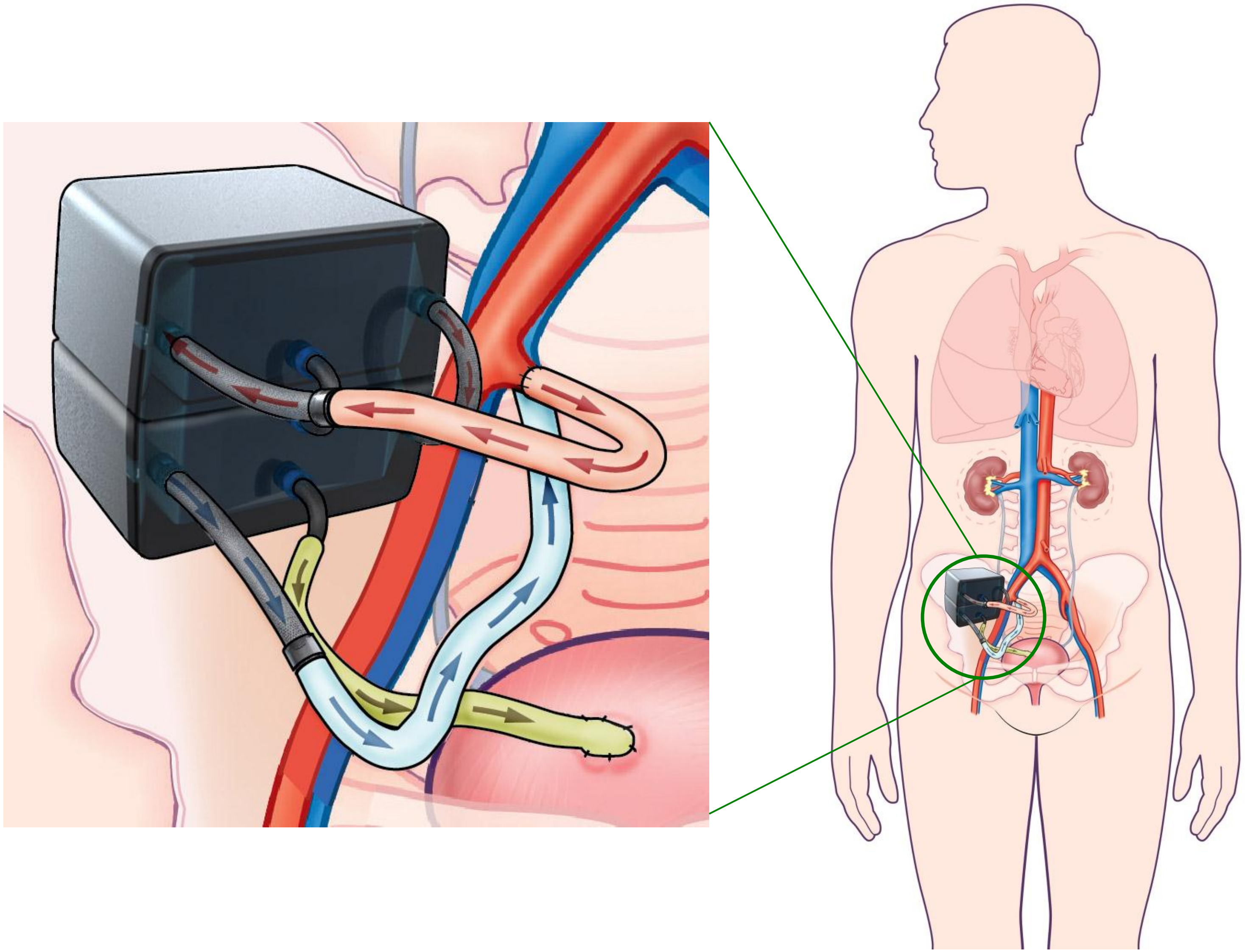
Implantable Bioartificial Kidney



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Device Benefits

- **Continuous treatment**
  - 24/7 operation eliminates build-up of toxins as happens now between sessions in standard dialysis
- **Freedom of mobility**
  - implanted device eliminates tethering to dialysis equipment
- **Decreased infection risk**
  - permanent vascular connection eliminates key entry path for pathogens
- **More physiological therapy**
  - bioreactor cells impart biological function that dialysis simply cannot
- **No need for anti-rejection drugs**
  - bioreactor cells are protected from patient's immune system

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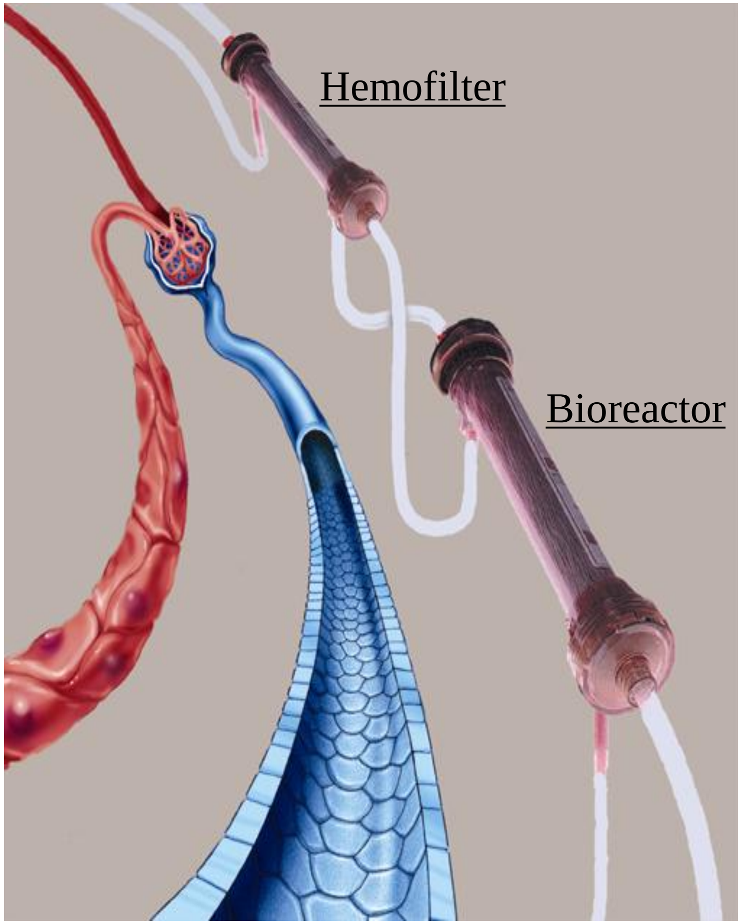
Renal Assist Device (RAD)

- **Extracorporeal circuit**
  - recapitulates nephron function
  - hollow fiber construct
    - commercial dialyzers
  - tissue engineered kidney
    - filtration + cell therapy
  - toxin removal
  - metabolic function
  - acute renal failure patients



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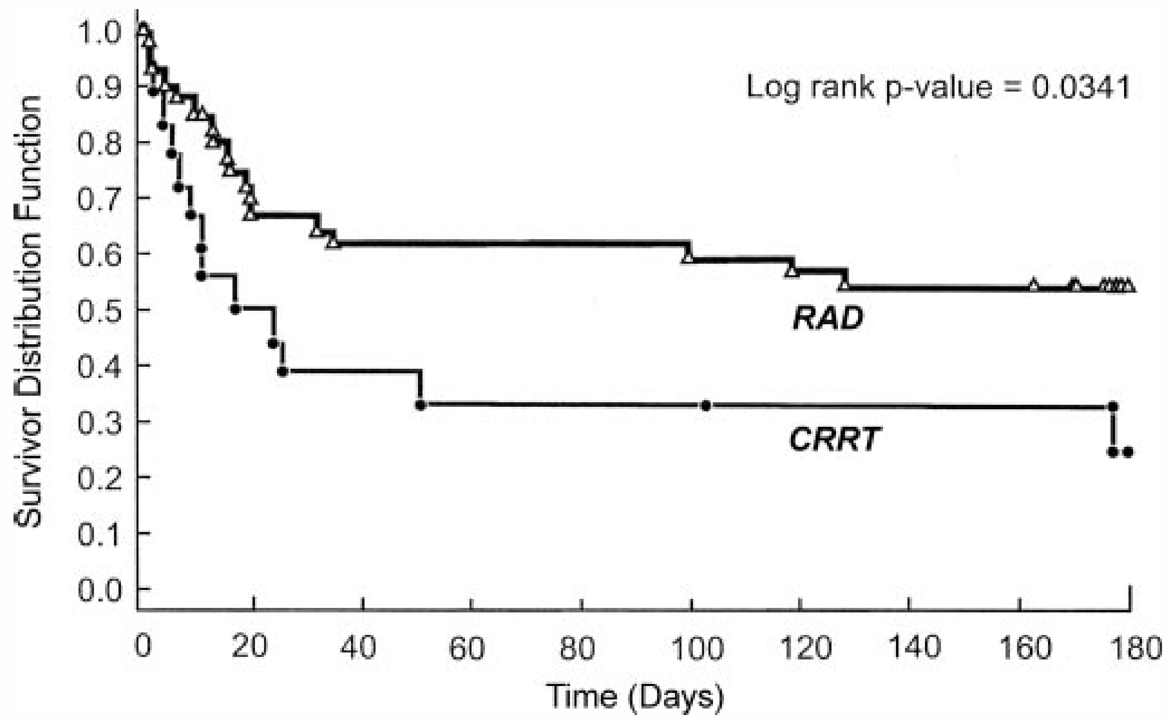
Clinical Testing Results

- **Phase II, multicenter, randomized trial with 58 patients in the ICU**
  - 50% reduction in mortality for patients treated with the RAD versus conventional therapy



Tumlin J et al. Efficacy and Safety of Renal Tubule Cell Therapy for Acute Renal Failure. JASN 2008 19: 923

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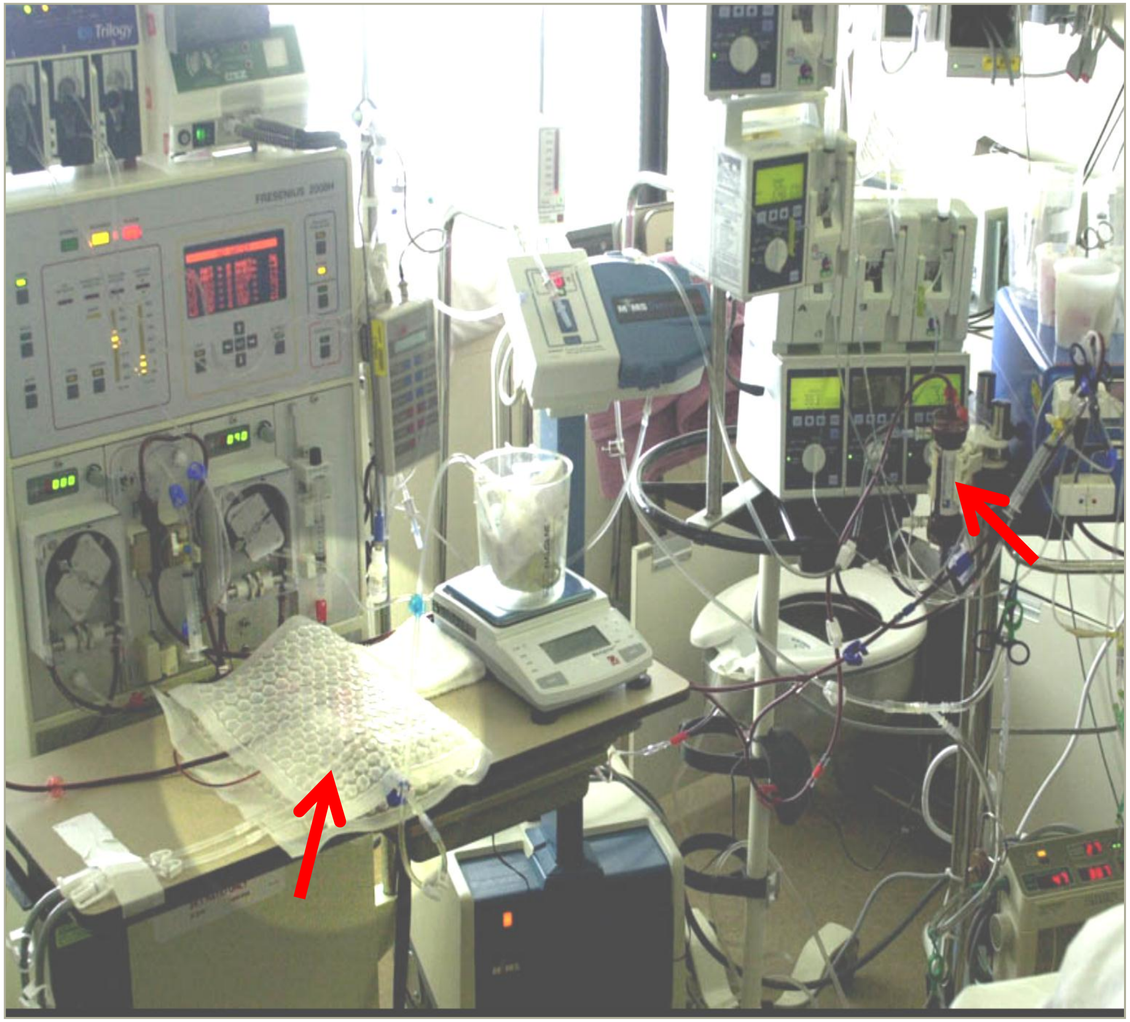
RAD Implementation



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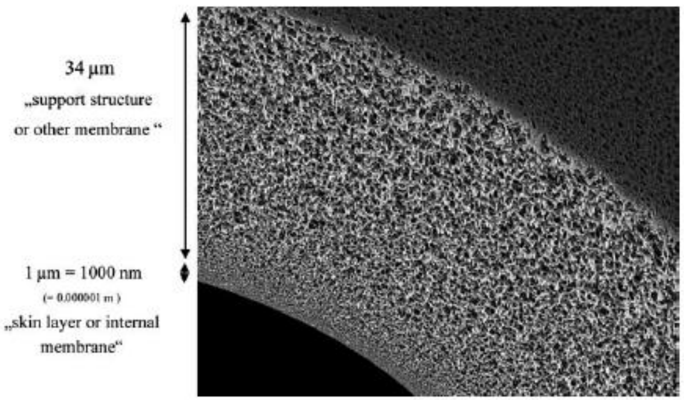
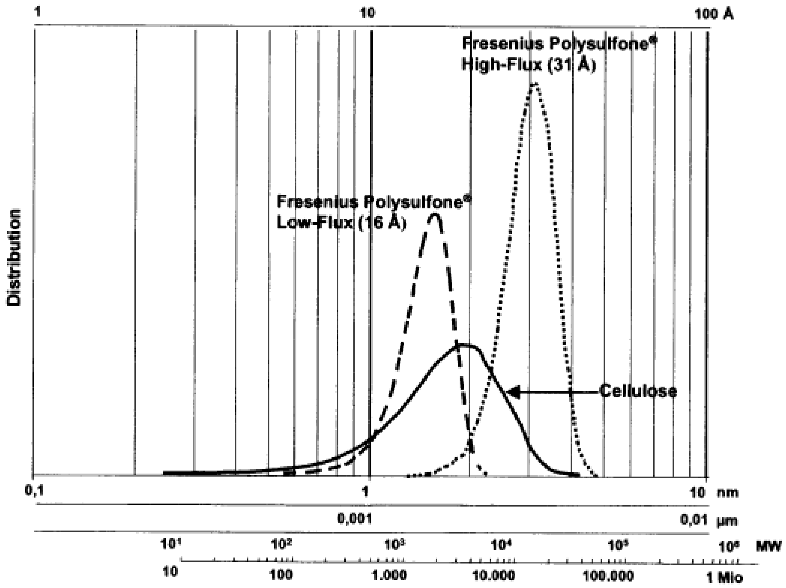
Fundamental Barrier to Miniaturization

- **Polymer membrane technology**
  - low hydraulic permeability
  - polydisperse pore size distribution
  - biodegradation

SEM – Polymer Membrane



Size Distribution Effects



Silicon Nanopore Membranes (SNM)

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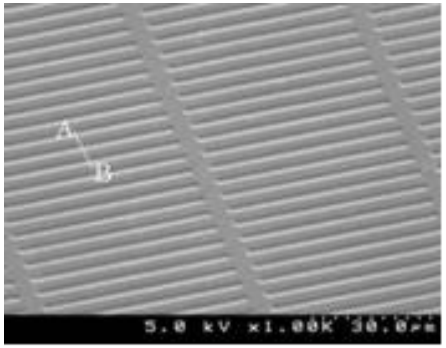
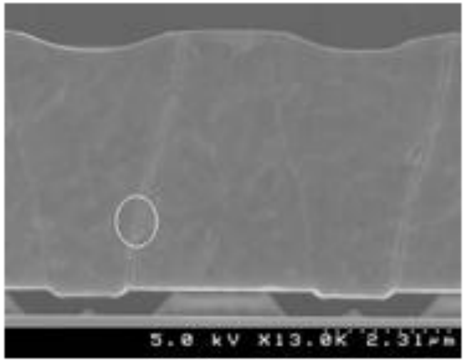
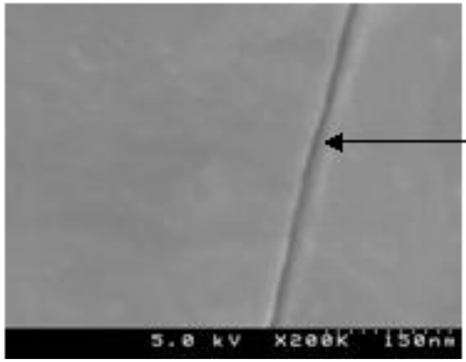
- **Monodisperse pore size distribution**
- **Chemical and mechanical stability**

SEM – Silicon Membranes







9 nm Pore
(x 200K)

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Kidney Project Team

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Development Strategy

- **Miniaturize RAD into implantable device by leveraging *nanotechnology* for hemofilter fabrication and scaffold design**
  - silicon nanopore membranes allow precise control of pore architecture
  - human kidney cells reabsorb salt and water while blocking back leak of uremic toxins
  - cells provide metabolic, endocrine, and immunologic functions

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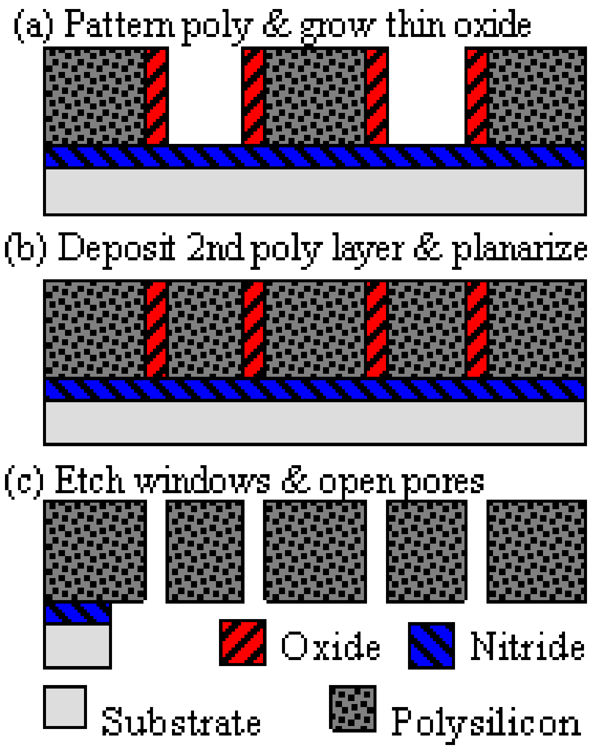
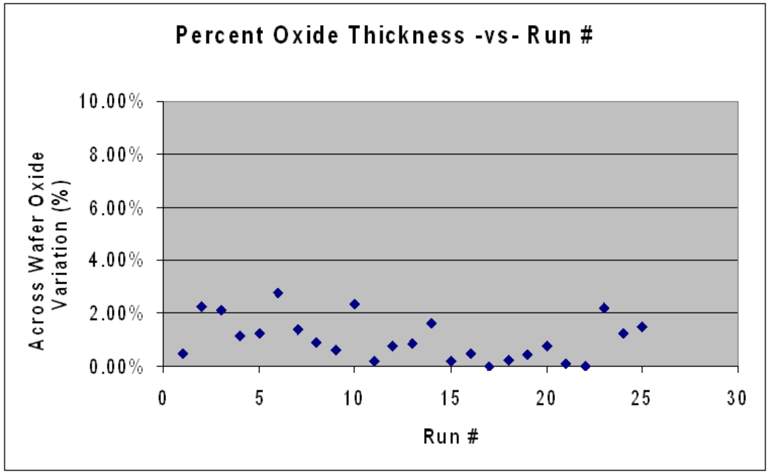
Membrane Fabrication

- **Novel process for reproducible fabrication of silicon membranes**
  - pore sizes: 5-15 nm
  - pore size variation: 1%





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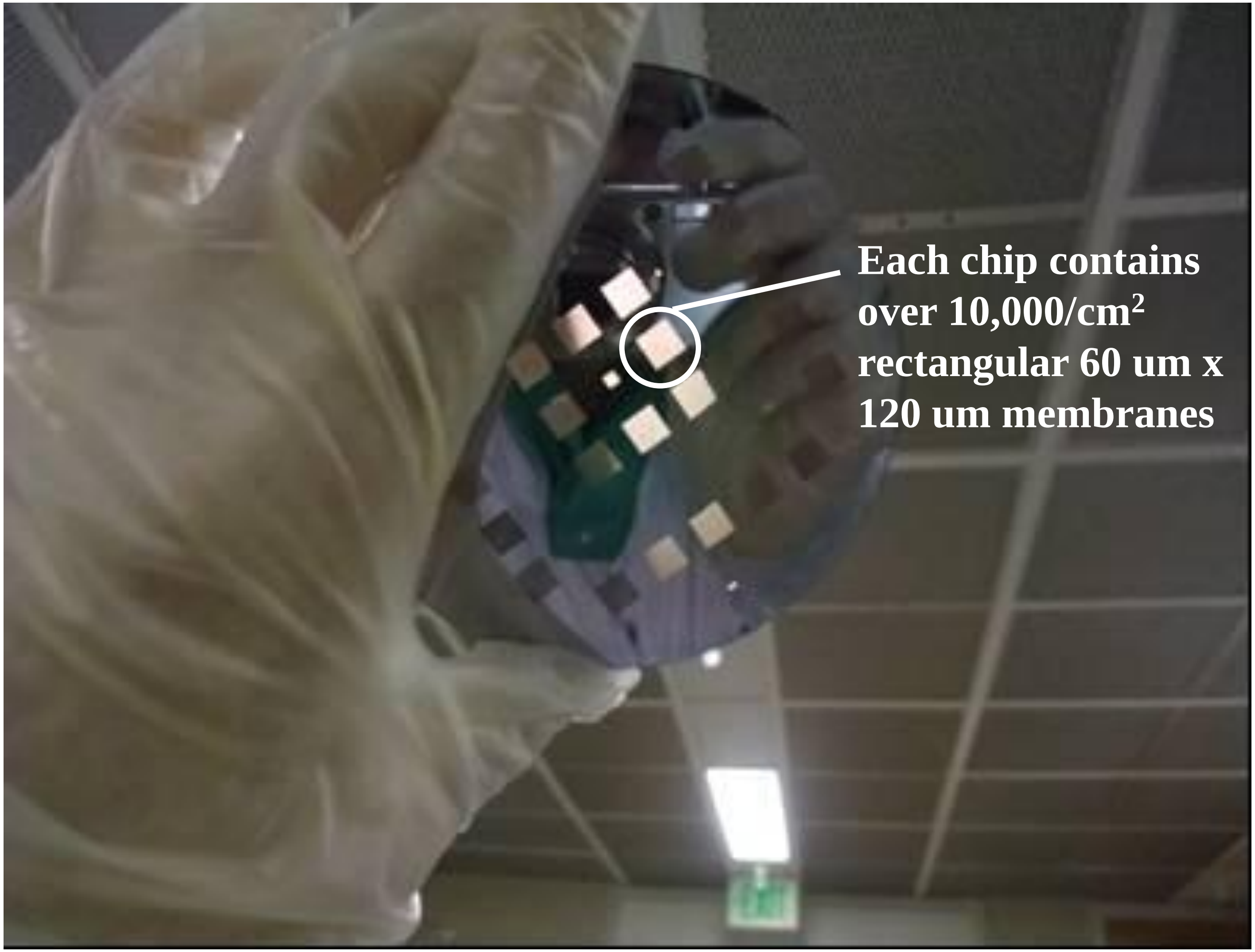
Completed Wafer



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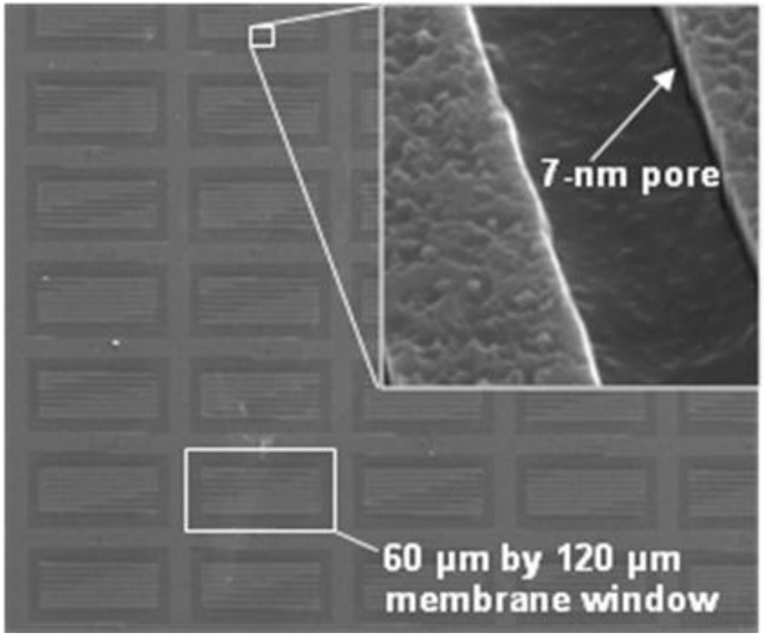
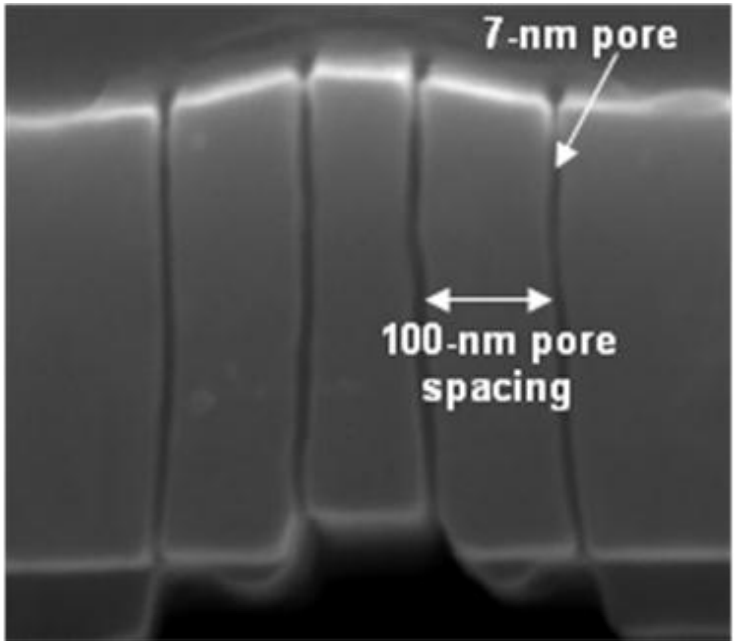
2nd Generation Membranes

- **High hydraulic permeability**
  - up to 600 ml/hr/mmHg/m^2
    - no pump needed
- **Manufacturing compatibility**
  - scalable for larger quantities





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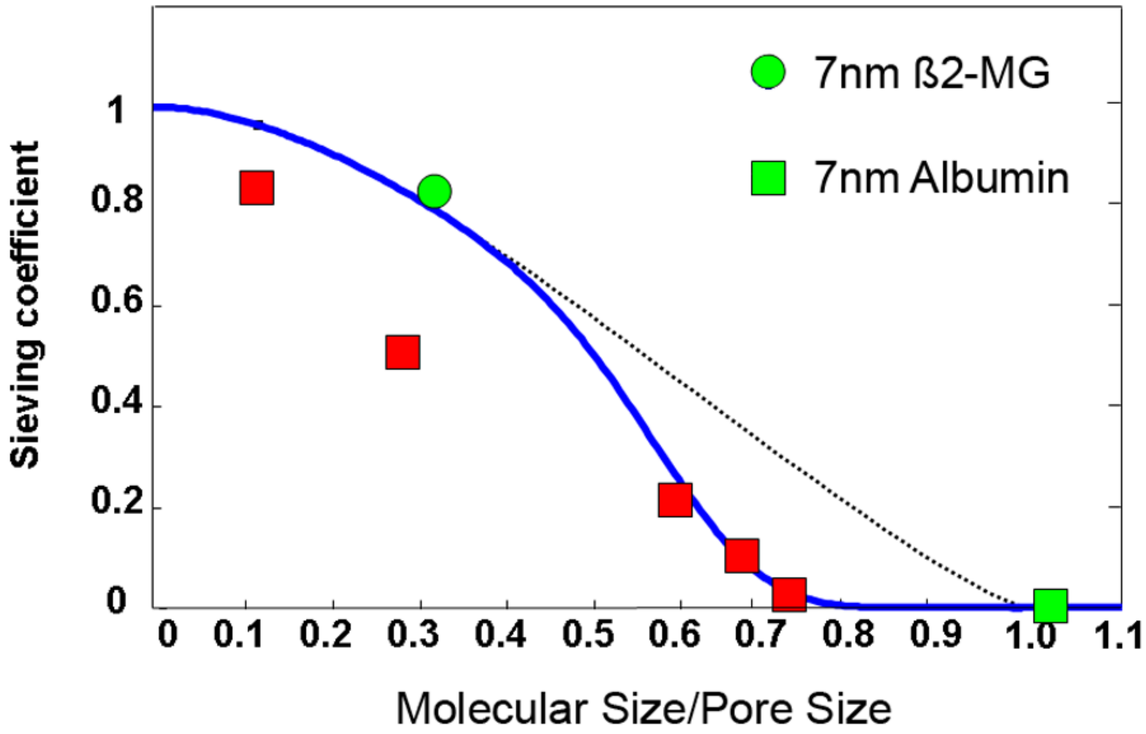
Membrane Filtration - Data



- **Selectivity for 7 nm pores**
  - albumin: <0.1%
  - beta2-microglobulin: >80%

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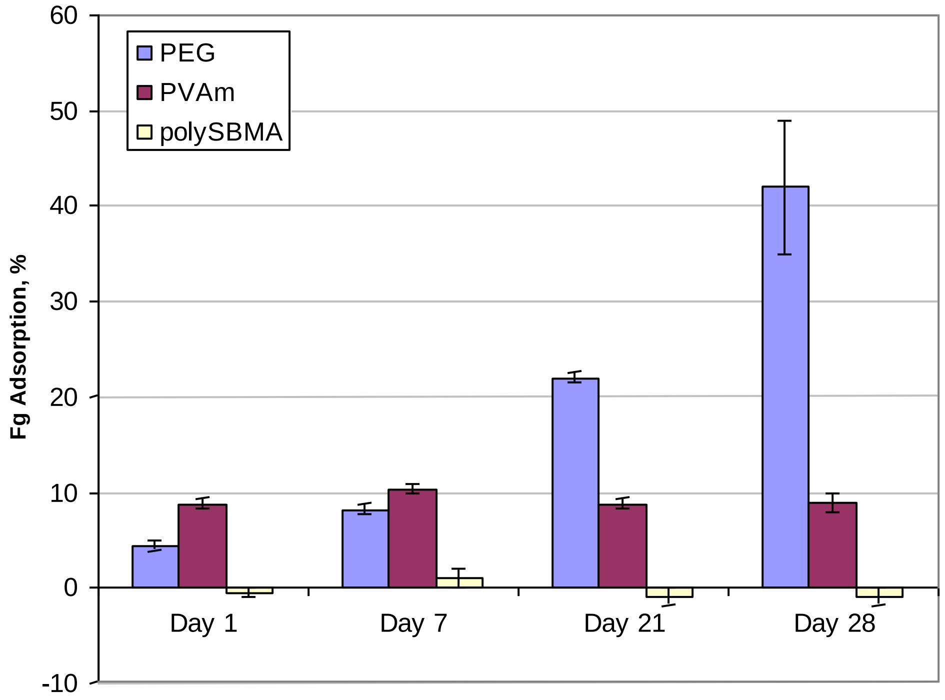
Anti-Biofouling Coatings

- **Evaluation of 3 coatings for protein resistance**
  - polyethylene glycol (PEG) is widely used
  - poly(N-vinyldextran aldonamide-co-N-vinylhexanamide) (PVAm)
    - synthetic glycocalyx
  - polysulfobetaine methacrylate (polySBMA)
    - zwitterionic polymer



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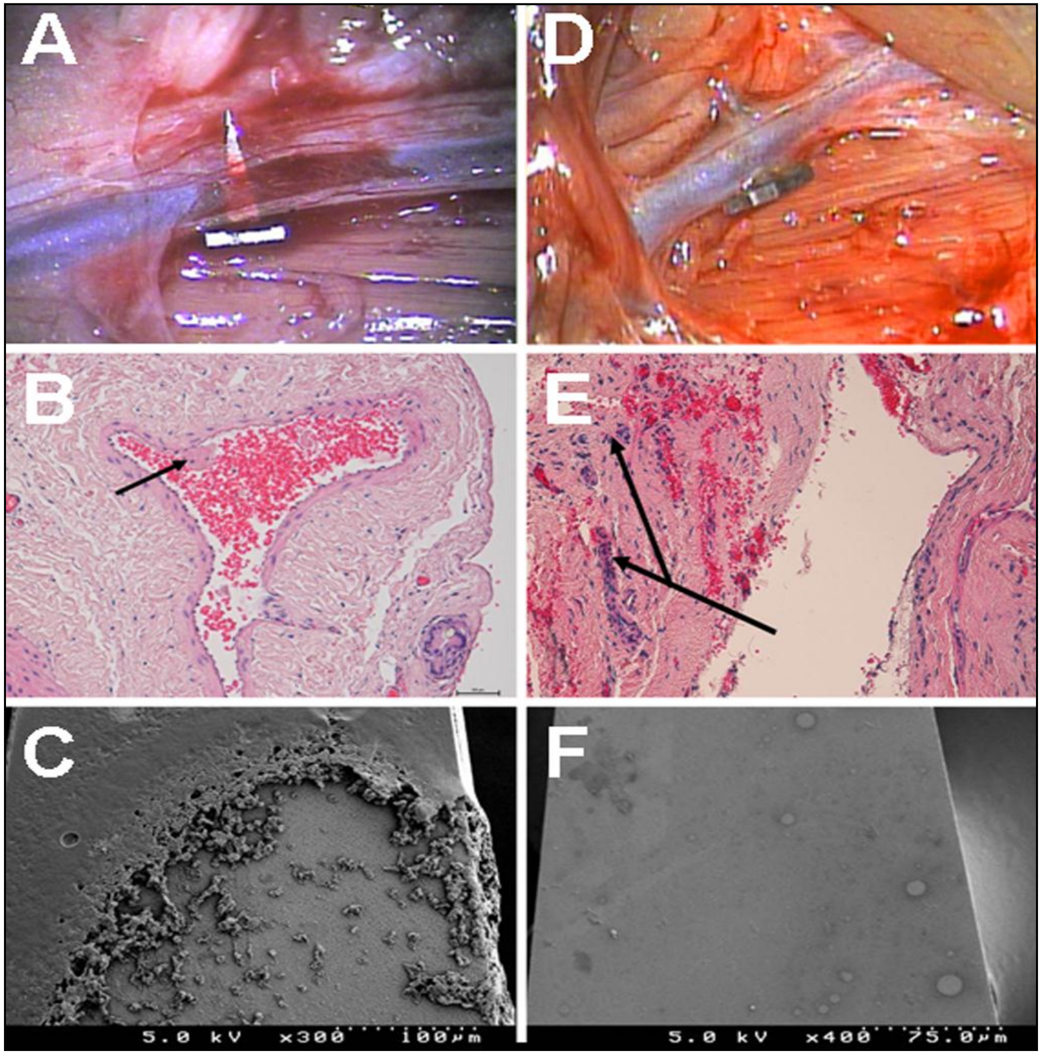
In Vivo Biocompatibility – 30 Days (Rat)

implant

bare Si

bare Si



explant

PEG/Si

PEG/Si

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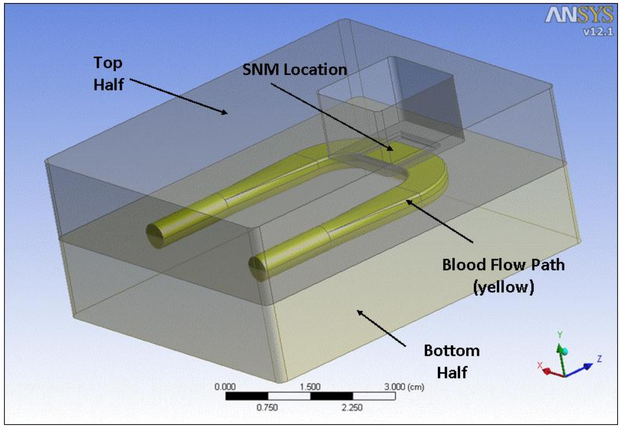
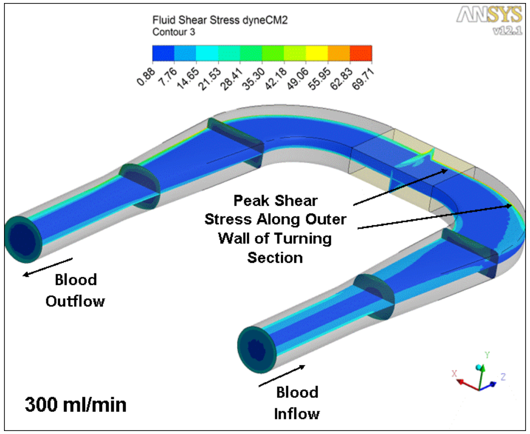
In Vivo Filtration

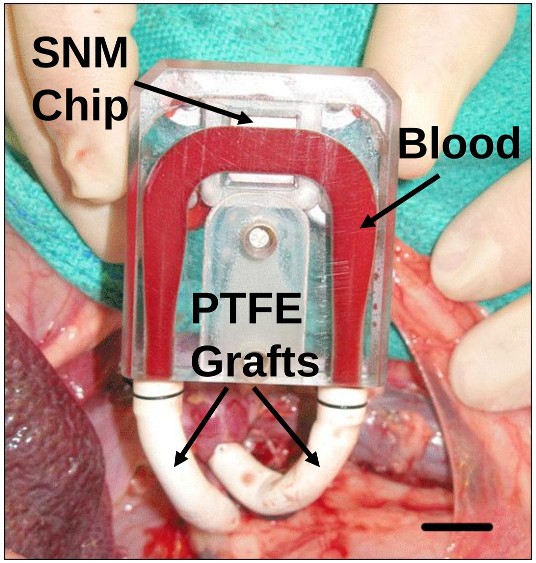
Hemofilter Cartridge Design

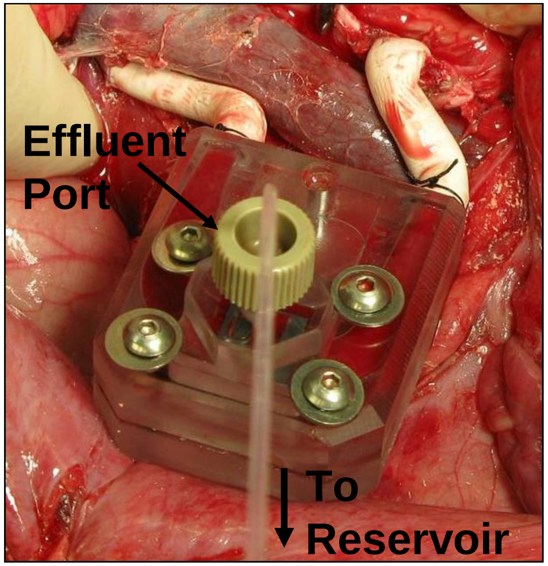


Flow Optimization



Mini-Pig Implantation





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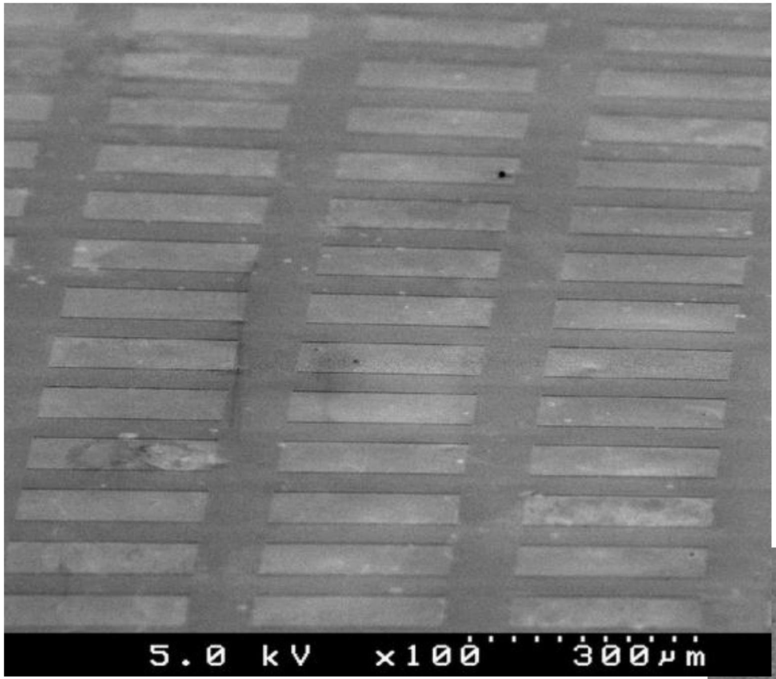
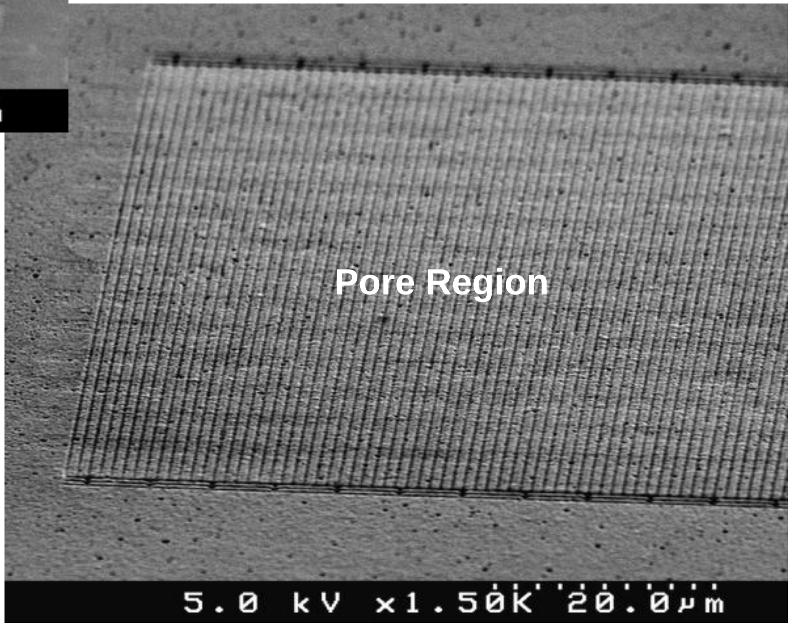
Membrane after Blood Exposure





Cell Sourcing and Storage

- **Isolation and expansion of cells from renal cortex**
  - "Enhanced Protocol" (EP)
  - 1 gm of biopsy tissue (10^{8-10} cells)
  - 17 doublings
  - 10^{13-15} differentiated cells: 1-100 acres surface area!
- **Successful cryopreservation of bioreactor**
  - differentiated cells *in situ*
    - >1 month
    - >4 months in storage

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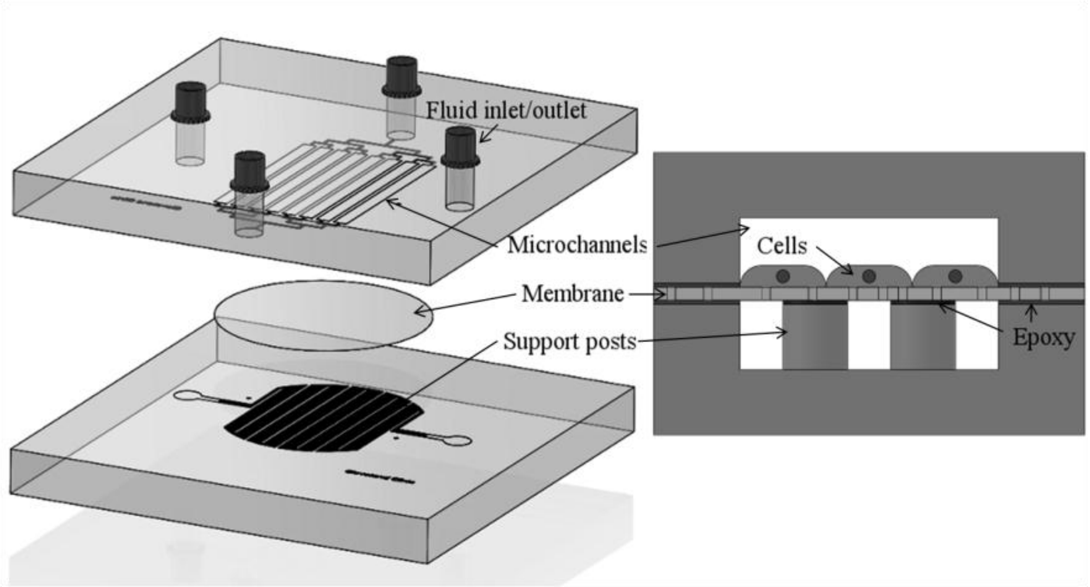
Cell Bioreactor



- **Bioreactor features**
  - microchannels for controlled shear stress on cells
  - membrane for cell support and transport pathway
  - basolateral chamber for membrane support and fluid collection

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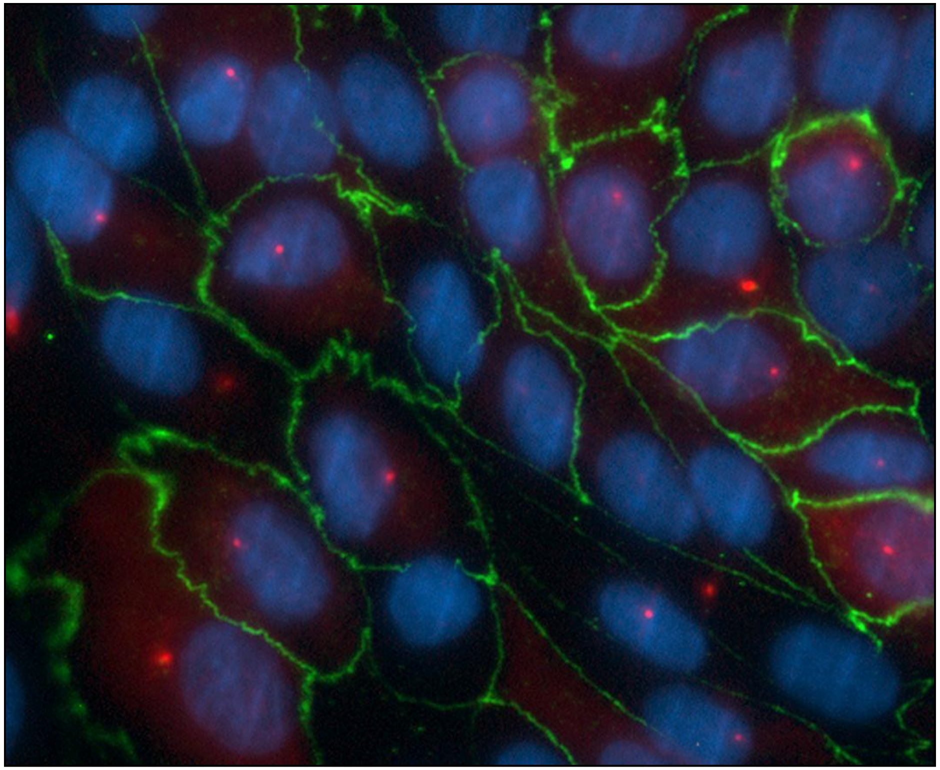
Cell Growth on Silicon Membranes



- **Human renal tubule cells (HRTCs)**
  - isolated from transplant discards
  - demonstrate differentiated phenotype

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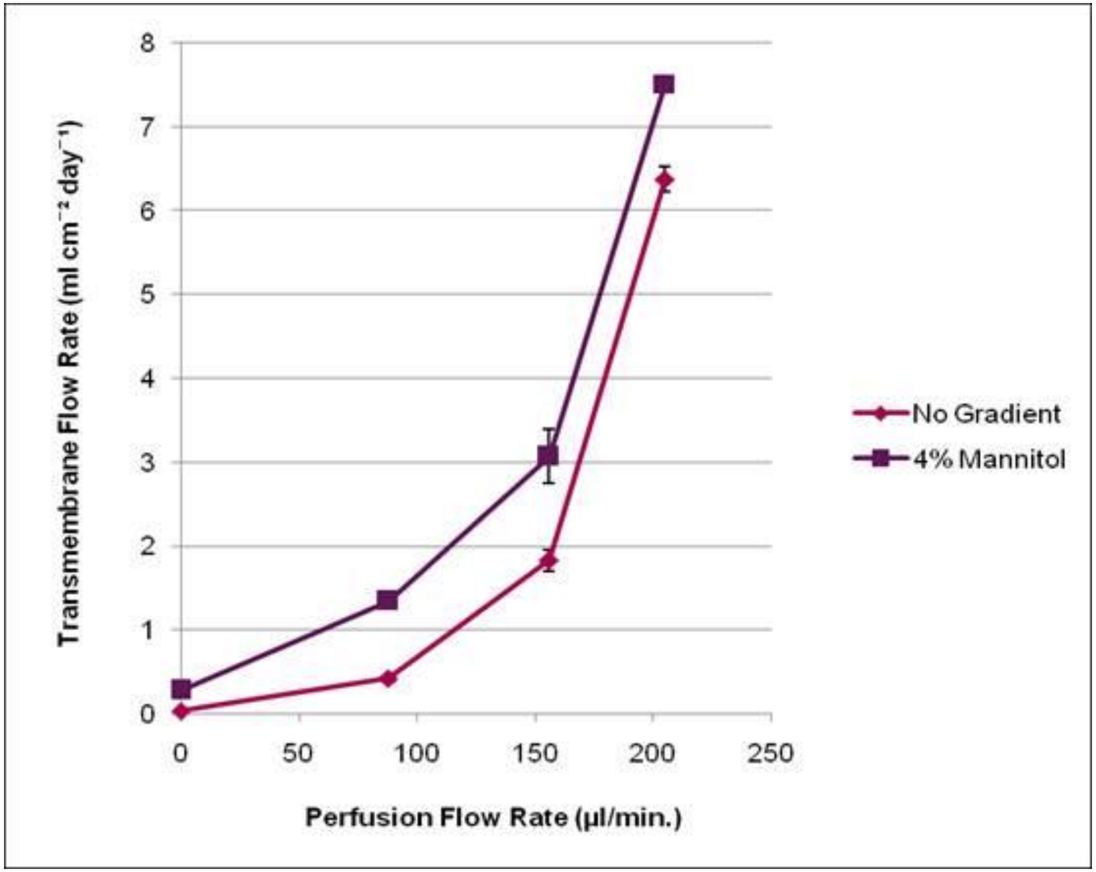
Active Fluid Transport via Cells



- **Increased transport under shear conditions**
  - translates to 70 liters/day/m^2

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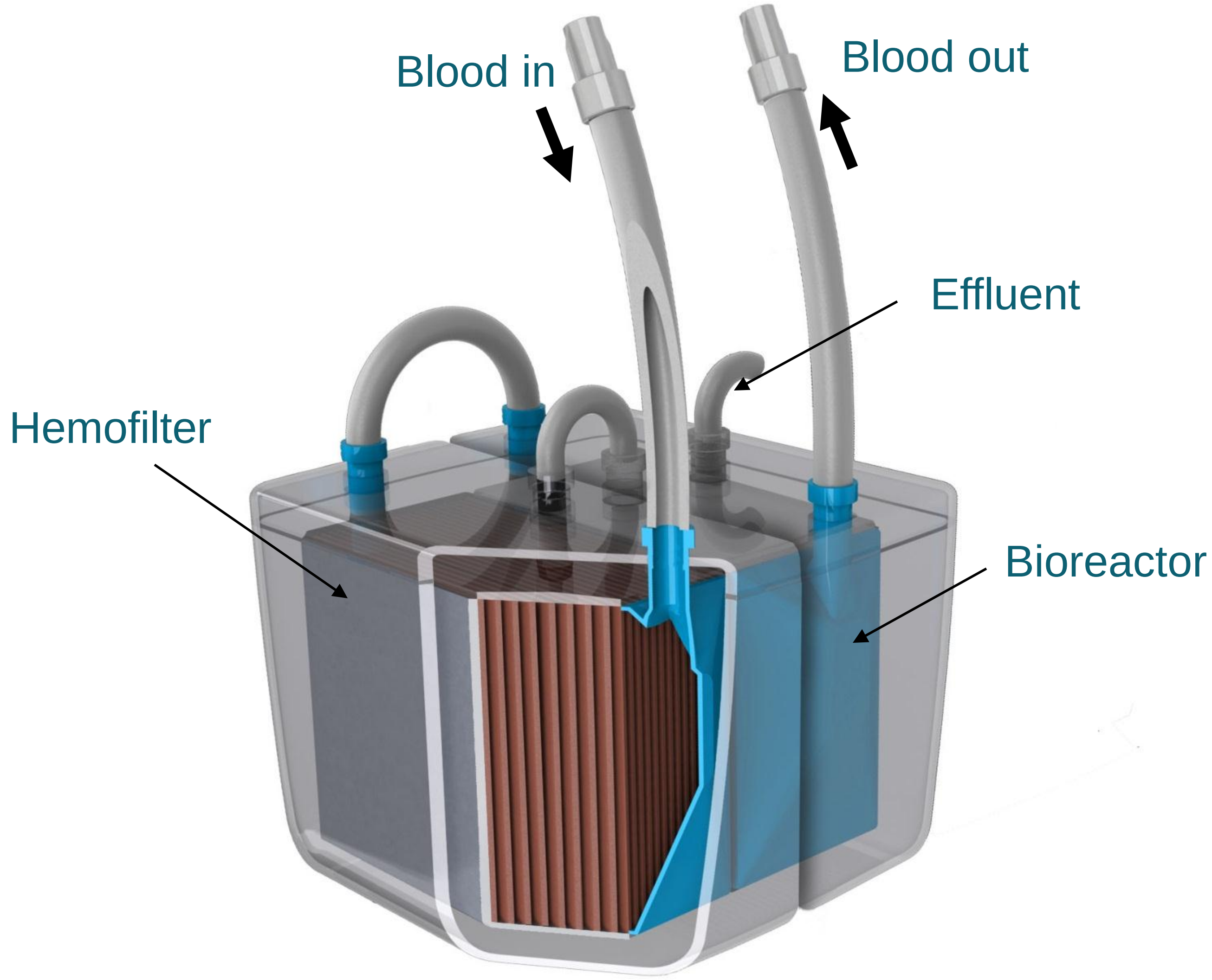
Key Accomplishments – Phase I

- **Silicon membranes**
  - high permeability
  - high selectivity
- **Biocompatible coatings**
  - protein anti-fouling
  - anti-thrombogenic
- **Cell sourcing**
  - harvest transplant discards
  - biopsy for autologous use
  - cryopreservation for storage
- **Cell performance**
  - significant immunoisolation
  - significant water reabsorption

iRAD – Phase II Device



Acknowledgements

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