Implantable Artificial Kidney: From Silicon Chips to Renal Clearance

*Financial Disclosure
Silicon Kidney LLC

ESRD Statistics

USRDS ADR 2015

Arrhythmia Care as a Paradigm
Application to Renal Replacement

The Renal Filter Unit: the Nephron

- Glomerulus: ~500,000–1,000,000 per kidney
- Proximal Tubule
- Loop of Henle
- Distal Tubule
- Collecting Duct

Generate ~150L of filtrate per day

Implantable Artificial Kidney
The Renal Filter Unit: the Nephron

- Glomerulus
- Proximal Tubule
- Loop of Henle
- Distal Tubule
- Collecting Duct

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

Solution - Implantable Artificial Kidney

Renal Assist Device

- Hemofilter

RAD Human Trial 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

Application to Renal Replacement

Key Target Specifications

- Package size no larger than 750 ml
  - no pumps
- Solute clearance of 20 ml/min (~20% of normal function)
  - membrane hydraulic permeability of 10 ml/min/mmHg/m²
  - ~30 liters of filtrate produced per day
- Selective filtration
  - Albumin loss of 3-4 G per day (membrane sieving coefficient of 0.025)
- Fluid excretion of about 3-5 liters/day
  - Requires reabsorption rate of 3 mmol/min Na⁺ in bioreactor
  - translates to ~25 liters of filtrate reabsorbed per day

The Renal Filter Unit: the Nephron

Optimizing Water Transport

Renal Tubule
- Selectively reabsorbs ~99% of most solutes
- Reabsorbs ~99% of filtered water
- Most reabsorption occurs in the proximal tubule
Optimizing Water Transport – Shear Flow

- **Bioreactor features**
  - Microchannel for controlled shear stress on apical surface of cells
  - Corning Snapwell membrane for cell support and transport pathway
  - Access to basal surface of cells for sampling

### Water Transport (LL-PCK1)

<table>
<thead>
<tr>
<th>Shear Flow in Dyne/cm²</th>
<th>Transport in ul/cm²/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.02</td>
<td>20</td>
</tr>
<tr>
<td>0.2</td>
<td>120</td>
</tr>
<tr>
<td>0.5</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>140</td>
</tr>
</tbody>
</table>

Cell Growth

- **Human renal tubule cells (HRTCs)**
  - Reliable isolation and expansion protocols
  - 1 gm of biopsy tissue \((10^8-10^9 \text{ cells})\) for 17 doublings

- **Successful cryopreservation and functional longevity**
  - 4+ months in liquid nitrogen
  - 6+ month cell viability in perfusion circuit

HRTC on Under Shear

4-month Cell Viability

The Renal Filter Unit: the Nephron

- **Glomerulus**
- **Proximal Tubule**
- **Loop of Henle**
- **Distal Tubule**
- **Collecting Duct**

Glomerular Filtration

~500,000–1,000,000 per kidney
Generate ~150L of filtrate per day
Filtration is a Fundamental Barrier to Miniaturization

- Current hollow-fiber filtration membranes have major limitations
  - thick porous polymer films have non-uniform pore sizes and degrade over time upon exposure to body fluids

SEM – Polymer Membrane  TEM – Glomerulus

Silicon Microfabrication

Precision patterning tools to enable high volume manufacturing of semiconductor devices

Completed Wafer

Each chip contains over 10,000/cm² rectangular 60 um x 120 um membranes

Membranes Characteristics

- High hydraulic permeability
  - up to 600 ml/hr/mmHg/m²
  - no pump needed
- Manufacturing compatibility
  - scalable for larger quantities
Biocompatibility Coatings to Prevent Thrombosis

- 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

![Graph showing adsorption percentage over time for PEG, PVAm, and polySBMA](image)

First Implanted Silicon Nanopore Membrane Hemofilter

Kensinger et al. *ASAIO J* 2016

First Implanted Silicon Nanopore Membrane Hemofilter

Titanium Hemofilter Prototype

Dimensions: 9.3cm x 5.7cm x 1.4cm

Ultrafiltrate Ports

3mm Blood Outlet

3mm Blood Inlet

Adapted from Kensinger et al. *ASAIO J* 2016
Individual Channel

- Nanopore Region
- Blood inlet: 1mm channel height
- Blood outlet
- Dimensions: 6.5cm x 3.2cm

Hemofilter Assembly

- Top Plate
- Assembled Subunits
- Seal Plate
- Bottom Plate
- Blood Inlet
- Blood Outlet

Whole Porcine Blood Bench Top Experiments

- Pump
- Blood Reservoir
- Inlet
- Outlet

Explant: Post-Operative Day 3 (POD3)

- Thrombus
Surgical Considerations for Implantation

• Housing material and geometry
• Device weight
• Vascular interface

Arterial Inflow (Dacron Graft)

Venous Outflow (Dacron Graft)

Device Placed in Retroperitoneum
Device Housing Modification

- Housing Redesign
  - 40% lighter by using Polyether ether ketone (PEEK)
  - Anchoring points incorporated into new PEEK plates

Surgical Considerations for Implantation

- Housing material and geometry
- Device weight
- Vascular interface

Vascular Connector Design:

- New Synthetic graft
  - More rigid material for the tubing with external support rings
- Strain-relieving Sleeve
  - External support to provide structural rigidity at the titanium-graft interface
Intraoperative positioning of modified prototype

Modified Vascular Interface

Key Phase I Accomplishments

- **Cell bioreactor**
  - reliable cell sourcing and expansion
  - successful cryopreservation
  - active water reabsorption

- **Hemofiltration**
  - high hydraulic permeability
  - high permselectivity
  - multichannel, large scale hemofilter implanted for up to 3 days

- **FDA Innovation Pathway 2.0**
  - CDRH program to shorten time-to-market
  - goal is to shorten time-to-market without sacrificing safety
Key Phase 2 Design Targets

- **Cell bioreactor**
  - Scale up of bioreactor for macroscopic filtrate reabsorption
- **Hemofiltration Longer scale implantation**
  - Optimization of porosity for increased hemofiltration
- **FDA Innovation Pathway 2.0**
  - CDRH program to shorten time-to-market
  - Goal is to shorten time-to-market without sacrificing safety

Acknowledgements

- **Collaborators**
  - The Kidney Project team
  - FDA CDRH
  - UCSF Pediatric Device Consortium
  - UCSF Surgical Accelerator
  - UCSF Clinical Translational Sciences Institute (CTSI)

- **Funding**
  - NIH: R01 EB014315; R01 EB008049; R21 EB002285; K08 EB003468
  - DoD: W81XWH-05-2-0010
  - NASA: JGBEC
  - Rogers Bridging-the-Gap Award
  - Hinds Distinguished Professorship II
  - Goldman Family Foundation
  - Wildwood Foundation