Portable Hemodialysis for Acute Renal Replacement Therapy

Jim McGrath and Alex Shestopalov

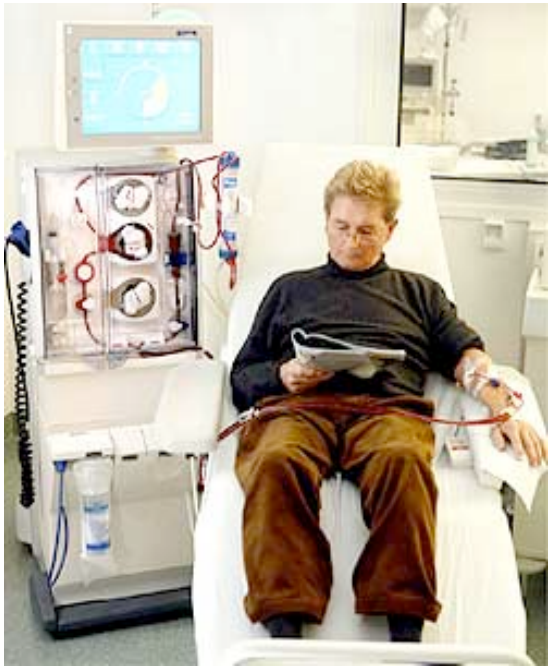
TDF Project Update
January 5, 2015

Team Members

- Jim McGrath (PI)
- Alex Shestopalov (UR, CHE)
- Dean Johnson (UR, Postdoctoral Fellow in BME)
- Xunchi Li (Doctoral Candidate, Chemical Engineering)

- Jeremy Taylor MD (UR, Nephrology)
- Louis DeVincenti and Kris Abrahams (UR Animal Medicine)

Project Vision



Center-based Dialysis
- 3-4 hours a day
- 3 times a week
- ~$750 per week

Wearable Hemodialysis
- Continuous and discrete hemodialysis
- Low flow rate to promote safety and well being
- Operating costs below Medicare bundle $
- $10B US market waiting for home HD

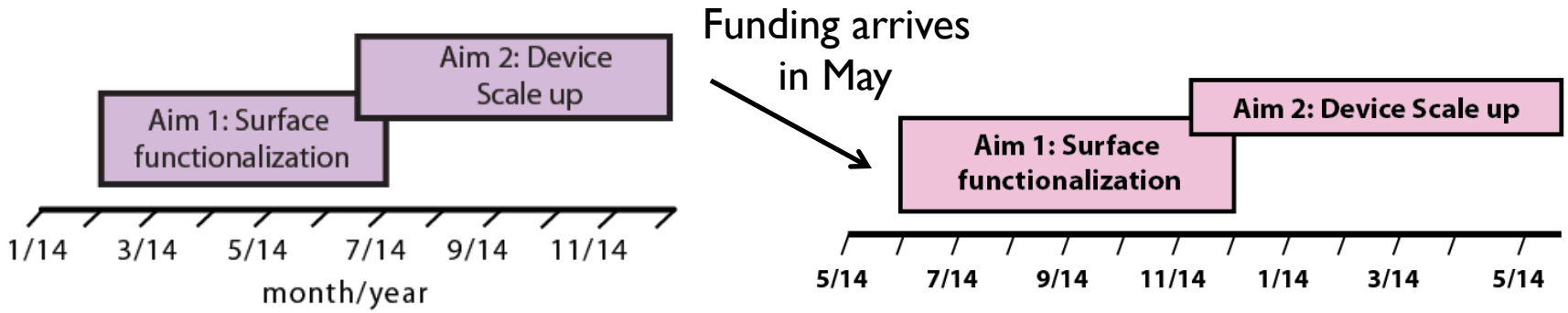
Original TDF Project Goals

Surface functionalization to prevent protein/cell binding

- Had previously achieved this and published using a proprietary technique from a commercial contractor
- Goal was to develop a process we controlled and understood – Alex Shestopalov

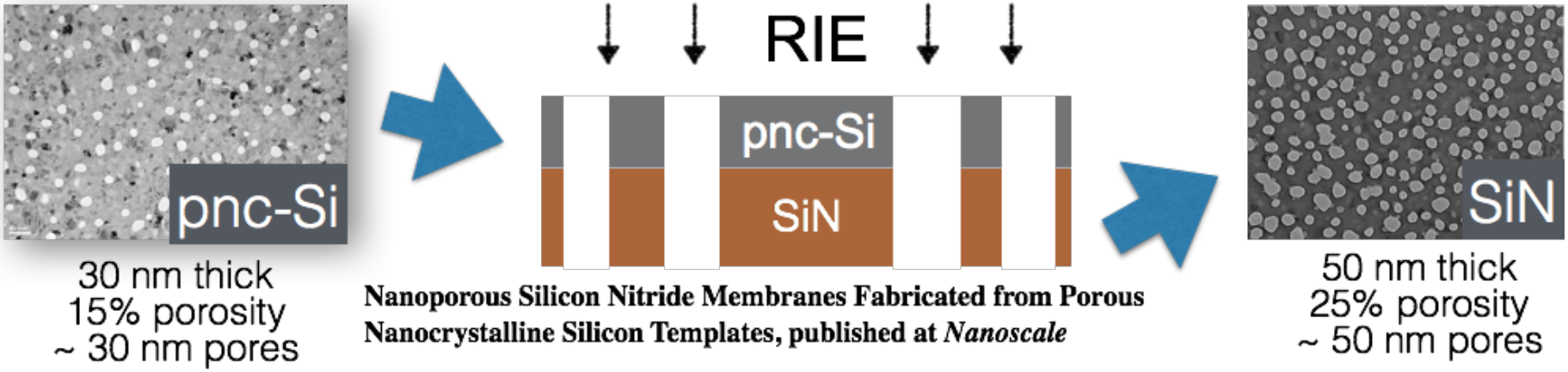
Scale-up for Large Animal Models

- Rat studies were planned
- Device fluidics and housing to integrate 10-20 chips to perform dialysis in large animals (pigs/sheep)



Key Developments

Nanoporous Nitride (NPN) replaces pnc-Si as membrane of choice

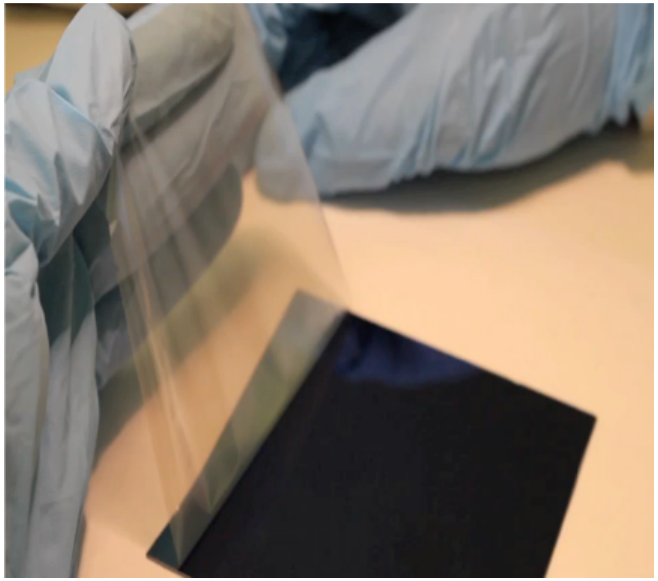


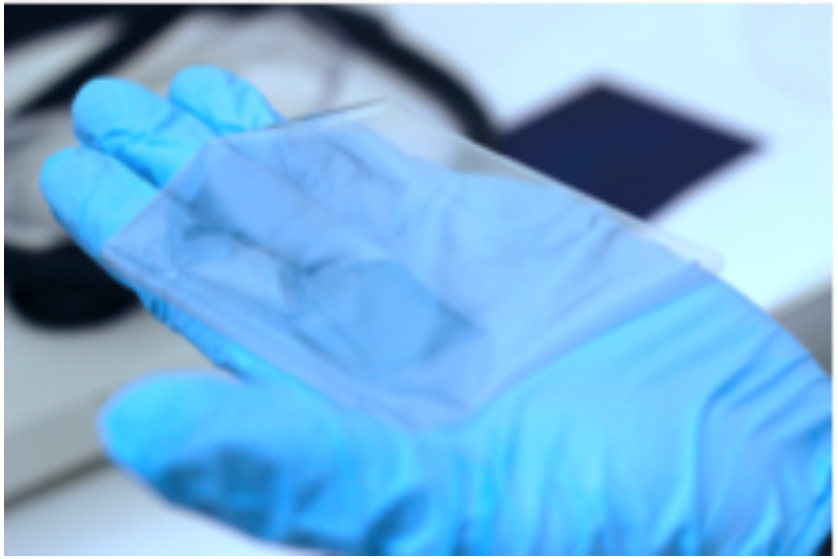
- Higher mechanical strength
- Enables higher surface area membranes
- Similar performance (resolution and permeability) as pnc-Si

Impact on TDF: need to functionalize SiN instead of pnc-Si

Key Developments

SiMPore/RIT membrane lift-off for microporous SiN membrane



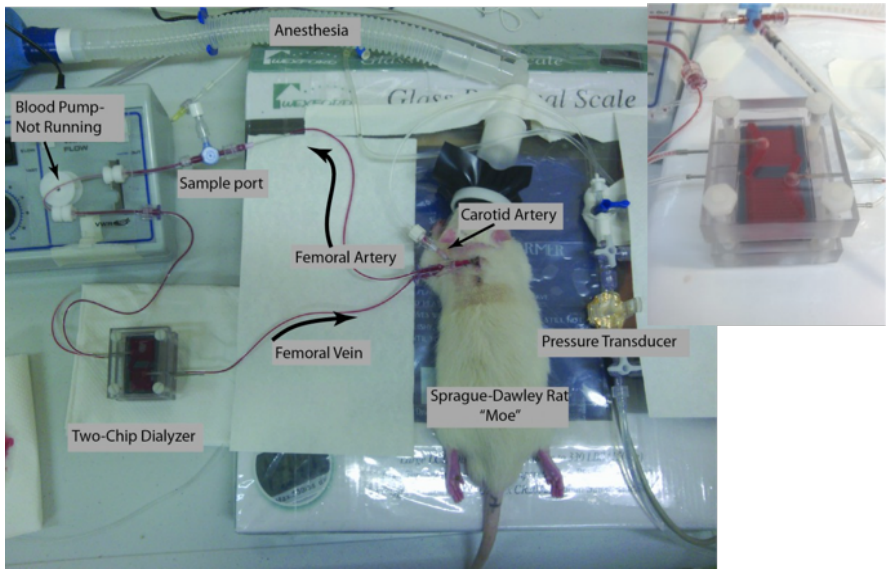


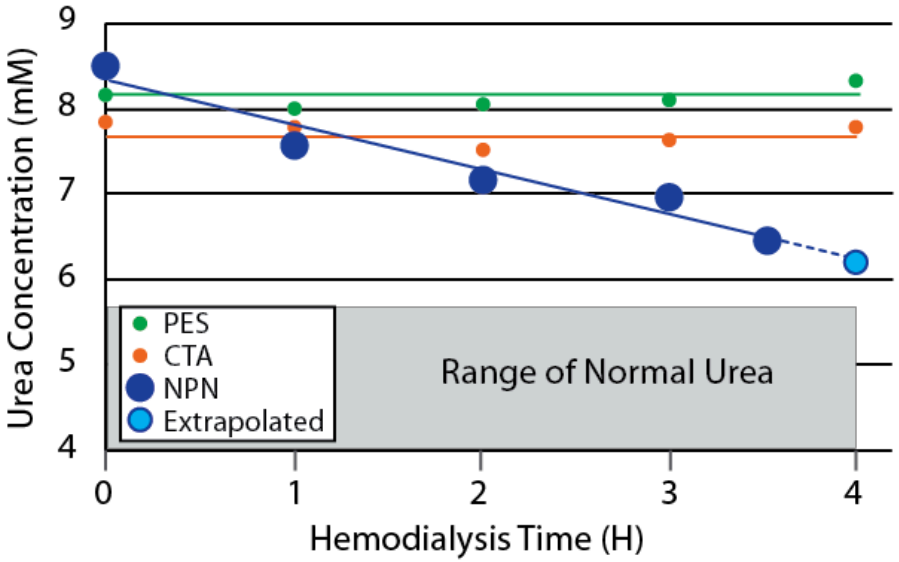
- Eliminates the chip-based membrane paradigm
- Enables sheet-based dialyzers >10x lower cost compared to chip-based solutions
- Coulter funds used to contract SiMPore to make nanoporous SiN lift-off

Impact on TDF: Simpler, cheaper device for large animal dialysis

Key Developments

Rat dialysis data implies membrane area need is 100 fold less than conventional membrane





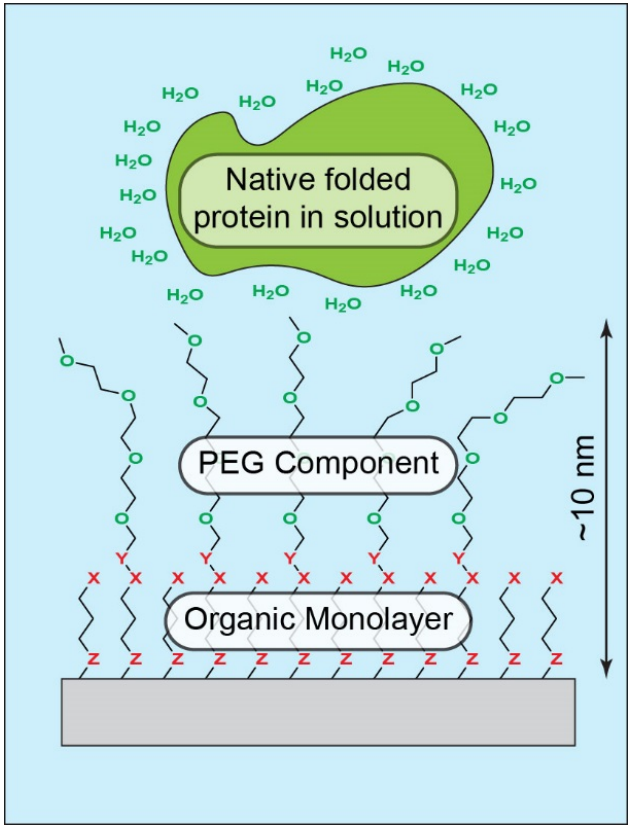
- Uremic rats returned to normal urea levels in standard dialysis time
- No improvement with conventional membranes in same format
- Conventional membranes require clearance with 0.66 cm^2 membrane area vs ~60 cm^2 for conventional membranes (Yorimitsu et al, 2013)

Impact on TDF: Large animal/human dialysis possible with ~2 lift-off sheets

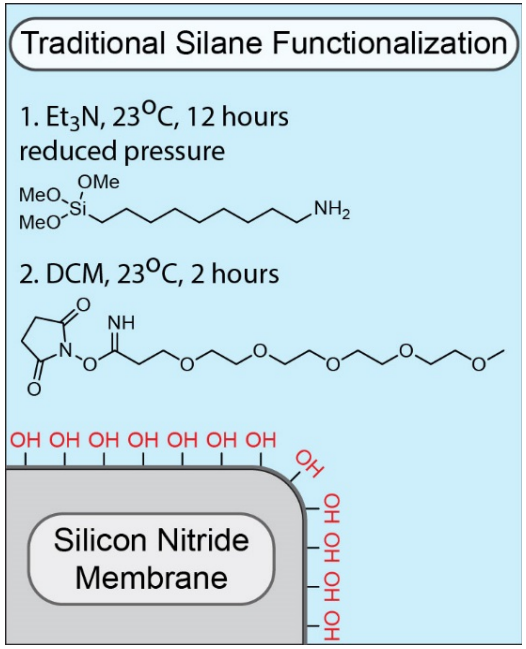
Functionalization to prevent protein binding on SiN

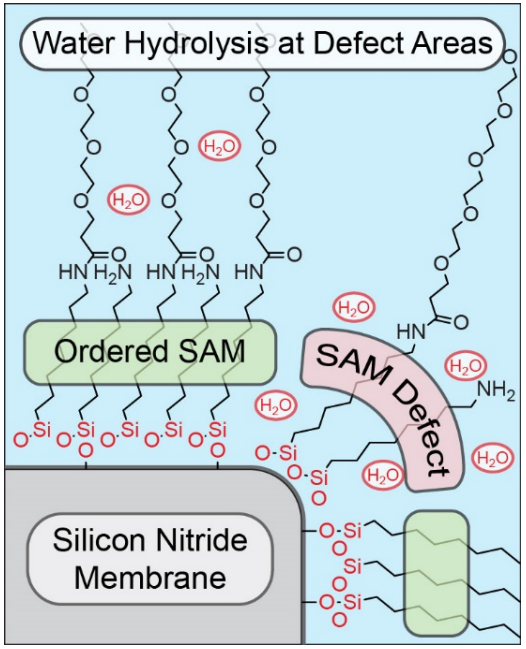
Requirements:

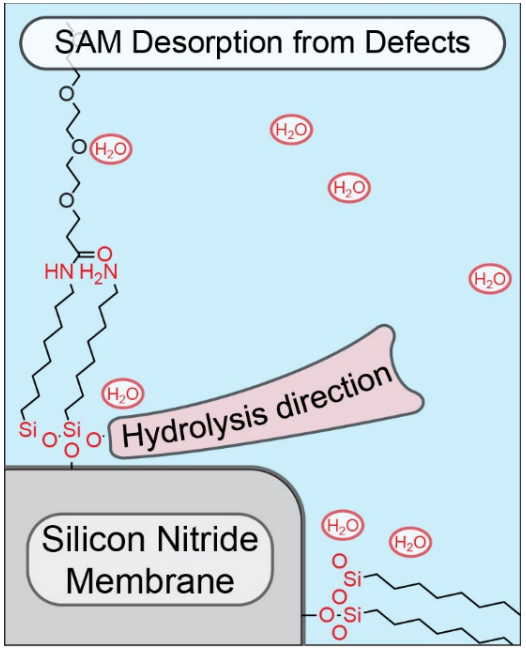
1. The length of the system <10 nm to avoid pore clogging
2. Stable attachment to silicon nitride, stability on curved interfaces, self-assembled phases that limit water diffusion to SiN vs non-hydrolytic covalent attachment
3. Amenable to vapor based deposition to enable scalable manufacturing on porous materials



Functionalization to prevent protein binding on SiN

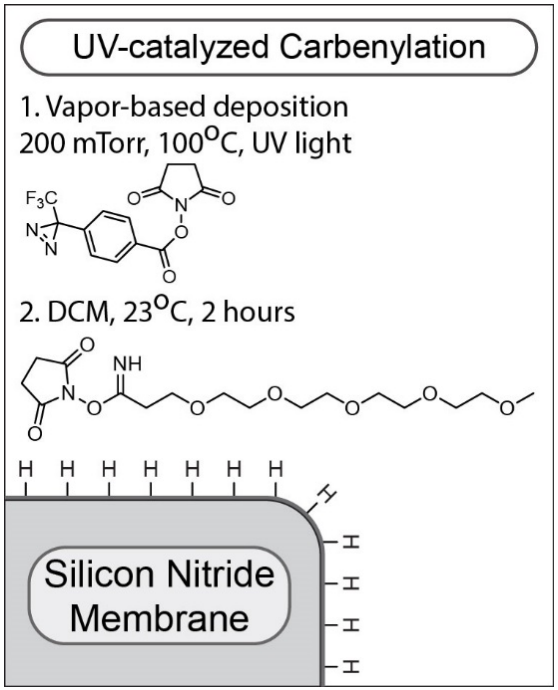


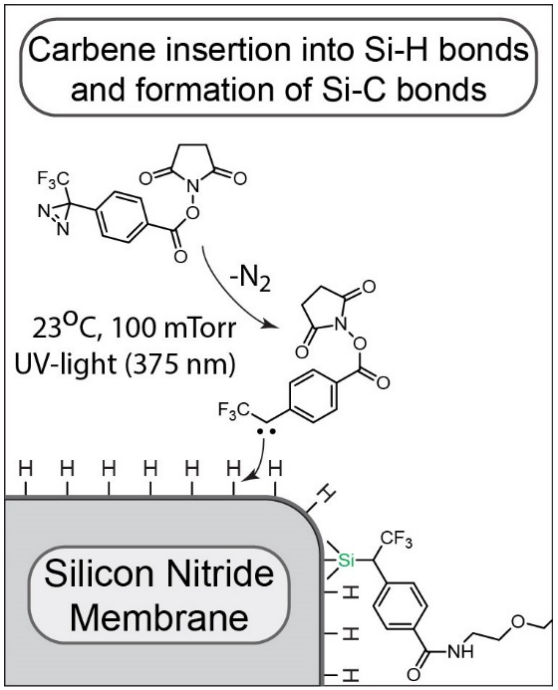


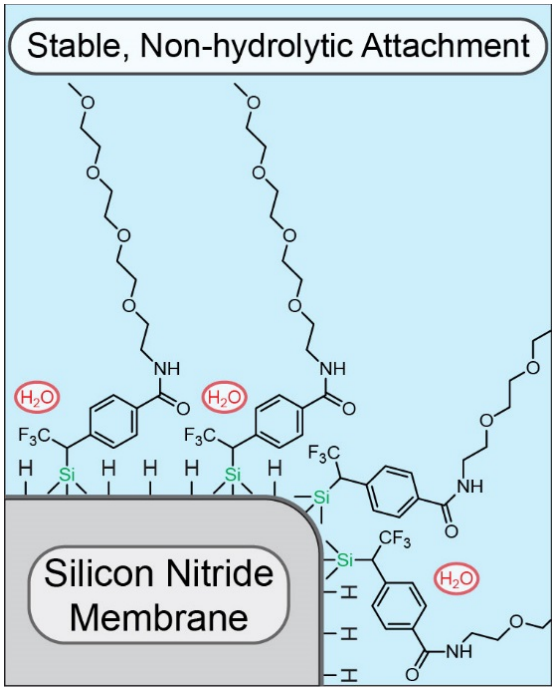


- Unstable in water
- Pores create defects that will accelerate hydrolysis
- Solution-based reactions compromise surface coverage and mechanical stability

Strategy





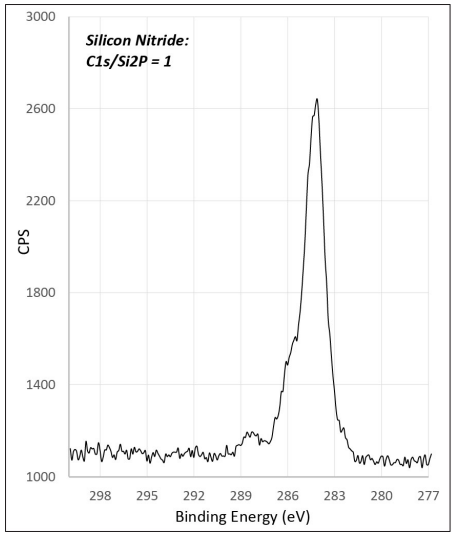


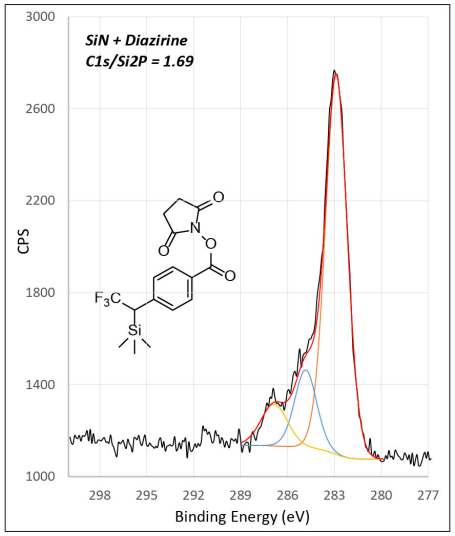
- Vapor-based carbenylation with diazirines is novel
- Vapor-based method will permeate porous materials and is scalable
- Potentially useful to modify any surface that has Si-H or C-H_3
- Stable in aqueous environments and curved surfaces
- Invention disclosure filed: **Monomolecular Organic Layer Deposition via Carbenylation of Hard and Soft Material Interfaces" #2-15060**

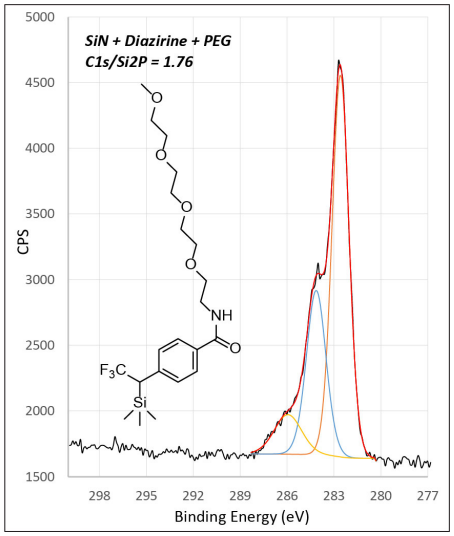
Metrics

X-ray photoelectron spectroscopy

- Electrons ejected from top ~10 nm of surface by focused x-ray beam
- Gives elemental composition of surface
- Used to verify functionalization and to measure protein binding







Contact Angle

- Convenient measure of surface modification and stability

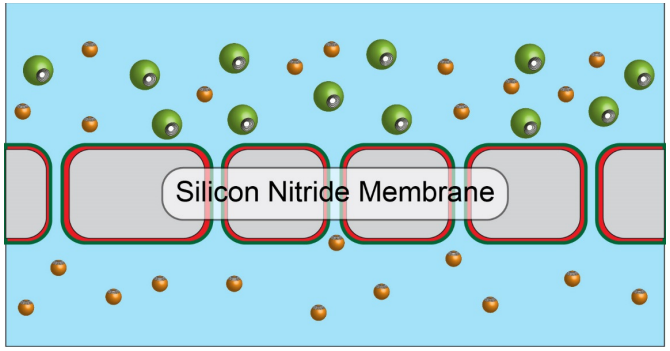
Fluorescent Protein Binding

- Alternative and convenient protein binding metric to confirm XPS

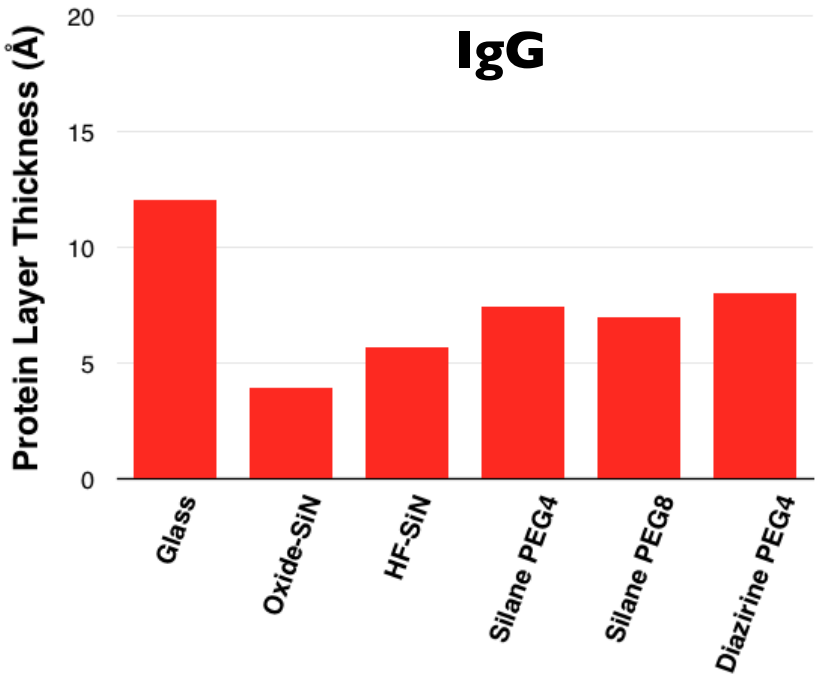
Electron Microscopy and Gas Permeance

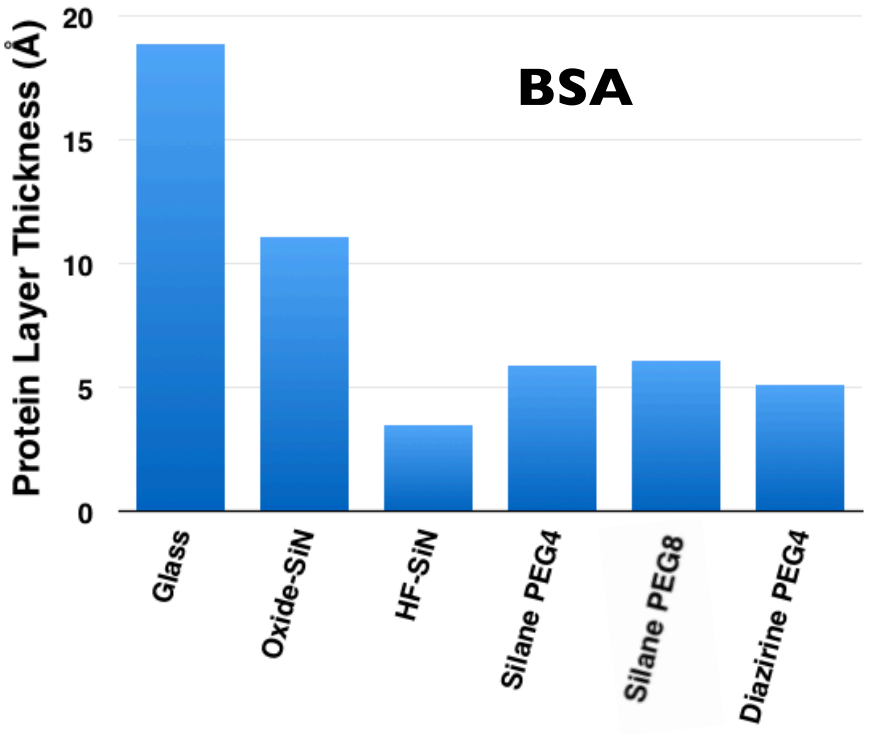
- Used to ensure pores are open

Results



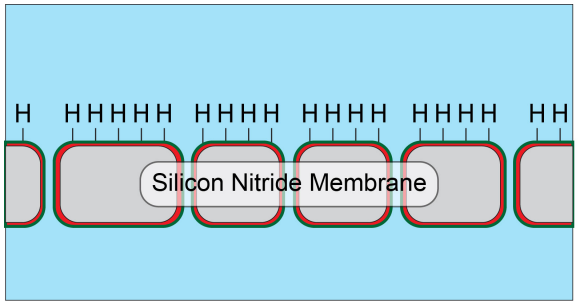
- Expose functionalized SiN and control surfaces to protein solutions (BSA & IgG 2 hours, RT in PBS)
- Use N/Si ratio in XPS as measure of protein binding
- Not shown: pores remain open, contact angles change

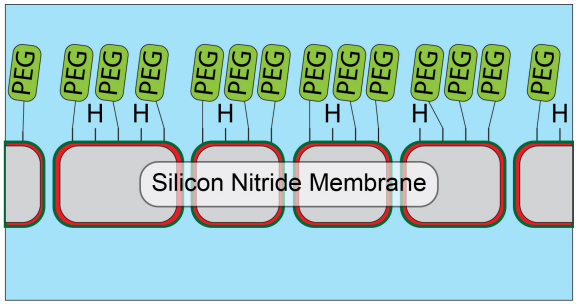




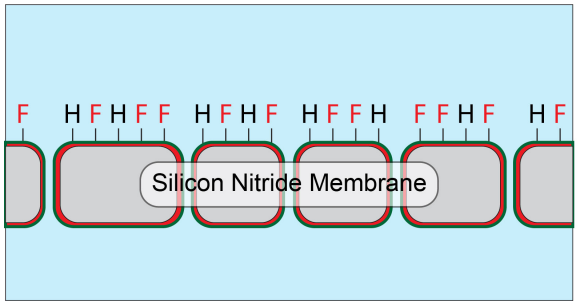
Results

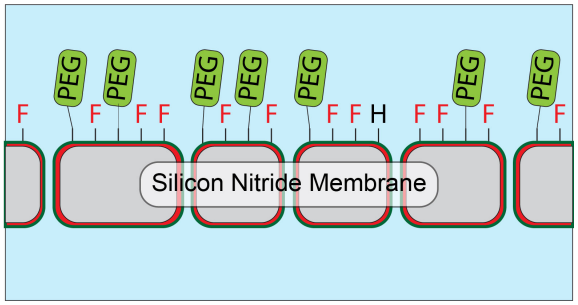
- Carbenylation results are similar to results with standard silane-based reaction with additional benefits of stability and vapor-based deposition. The thicknesses of the molecular coatings are below 1 nm.
- The thicknesses of the non-specifically adsorbed protein layers are below 1 nm. No pore clogging is observed after the functionalization or adsorption experiments
- We suspect Fl-molecules left from HF pre-treatment are reducing surface density of PEG molecules





Ideal Surface





Actual Surface

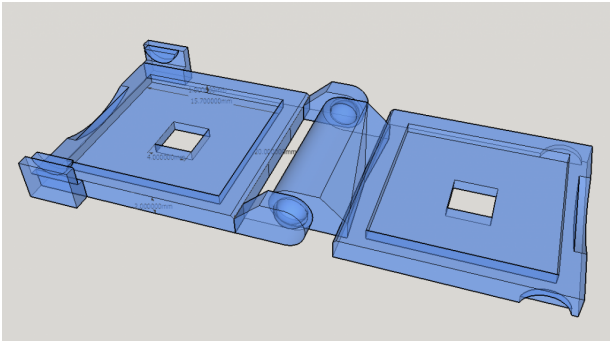
TDF Plans for 2015 (January –> June)

Functionalization

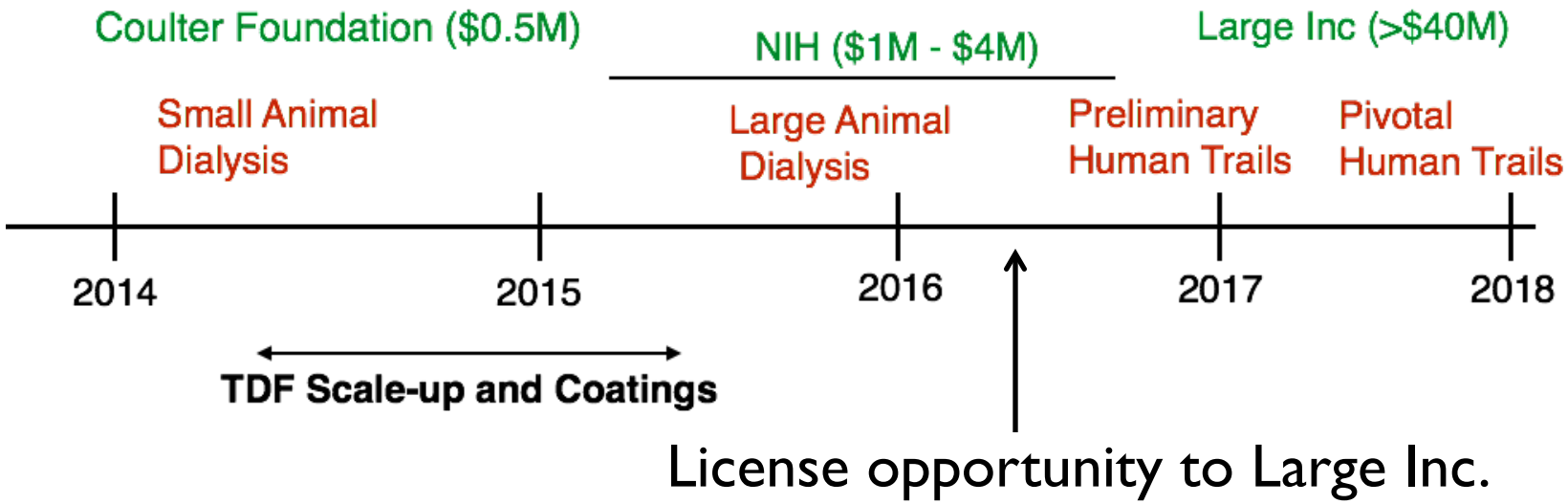
- Use BOE etch to increase the density of the PEG molecules in the carbenylation approach
- Explore carbonization technology developed by McGrath and Fauchet to create stable sublayer for the carbenylation and PEG attachment
- Long-term adsorption studies.
- Correlate XPS measurements of the protein thicknesses with traditional fluorescent measurements.
- Biocompatibility studies (protein and cell activation studies)

Scale-up

- Scale up vapor-based carbenylation to wafer-size substrates
- Incorporate lift-off sheets in 'clam-shell' devices for large animal dialysis
- Benchtop dialysis of urea clearance in clam-shell devices



Commercialization Timeline



Budget

Installment 1 (May-Dec): Requested $20,668; Received $22,263; Unspent ~$6,000
Installment 2 (Jan – July): $27,737

Installment 2: January 15, 2015 - July 15, 2015

Personnel	Effort	Salary	Fringe	Total
McGrath Post Doc	50%	$45000	27%	$14288
Shestopalov Grad Student	50%	$25000		$6250
Membranes				$6000
Materials/Devices				$4000
Core Facilities				$3000
TOTAL				**$33538**