Evolution of AV Graft Technology

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Disclosures

- No financial Disclosures

Global Increase in AVG use for Hemoacess

- Increase in elderly population
- Increase in Diabetic nephropathy and diseases associated with Diabetes
- Long term patency and complications still remains inferior when compared to autogenous fistulas

Reasons for loss of Patency of AVG

- Neointimal hyperplasia (NIH) development as graft-vein anastomosis
- Compliance mismatch
- Procoagulant state, responsive to graft material and flow dynamics
- Occlusion and thrombosis
- Graft material degeneration from continued puncture

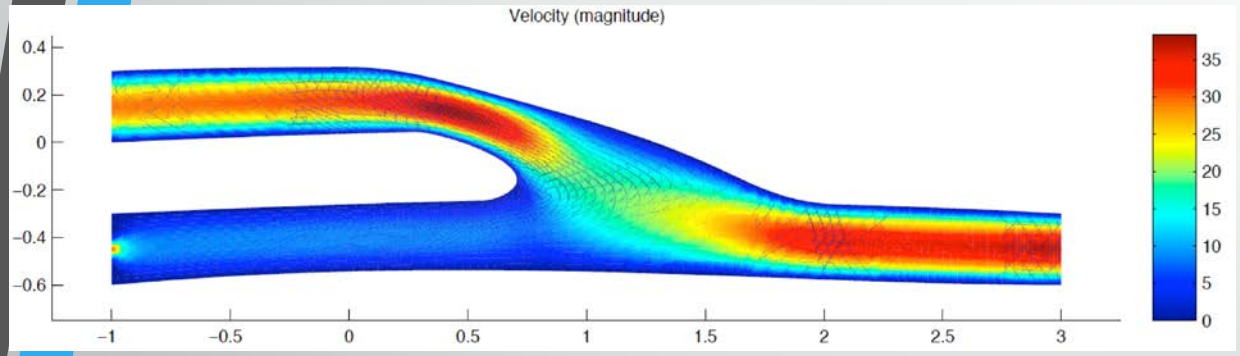
Graft modification strategies to improve patency of AVGs

- Graft Material—Biologic vs man made material
- Graft Geometry
- Graft coating
- Graft Surface technology
- Tissue Engineering

Graft Material

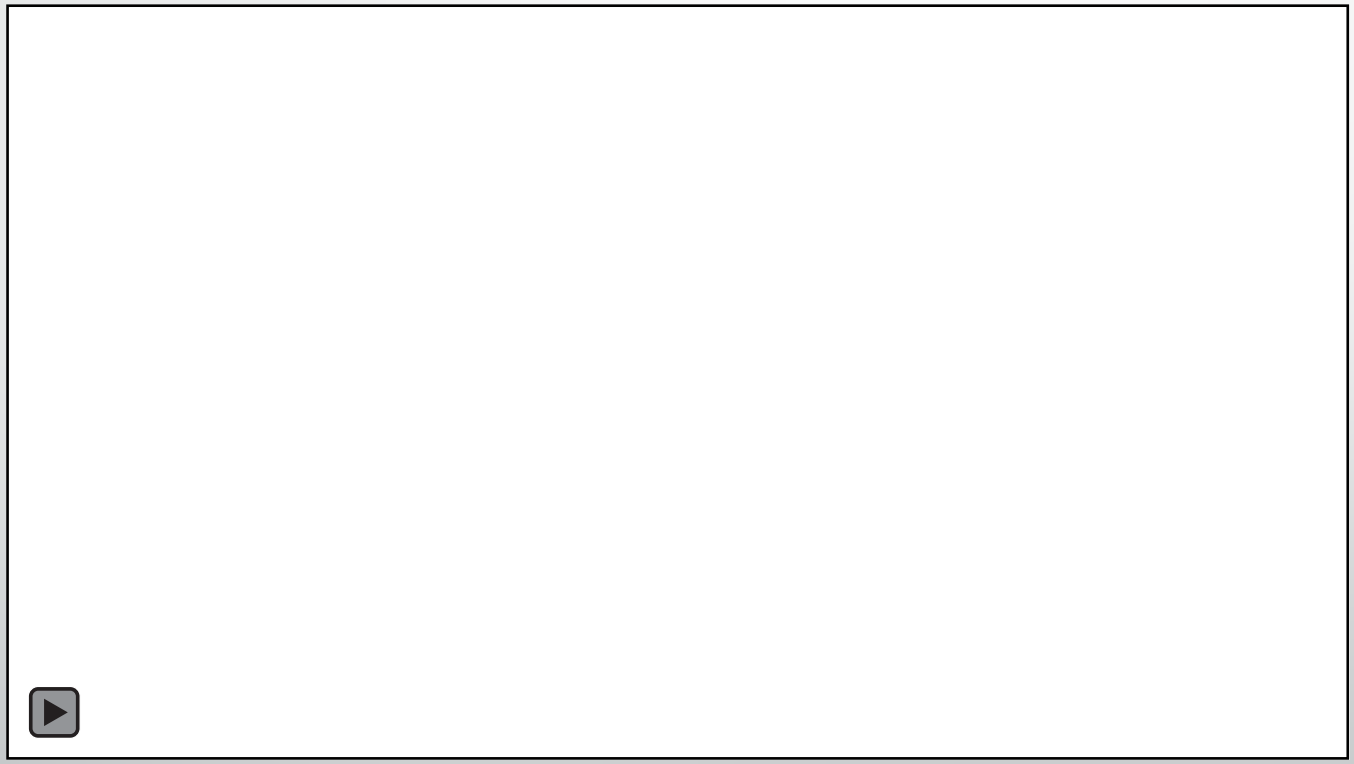
- Expanded Polytetrafluoroethylene (ePTFE)
- Polyurethane urea
  - Equal patencies between the two materials
  - Early access of Polyurethane urea and early access of novel changes to ePTFE
  - ePTFE graft still remains the major material for AVG delivery

Graft Geometry and Flow Modulation



- Wall Stress and Turbulent Flow with oscillating flow patterns are pathogenic factors in development of NIH
- Attempts to manipulate graft hemodynamics to establish a laminar flow pattern in order to reduce NIH

Computational Fluid Dynamics and Simulation



Graft Geometry and Flow Modulation

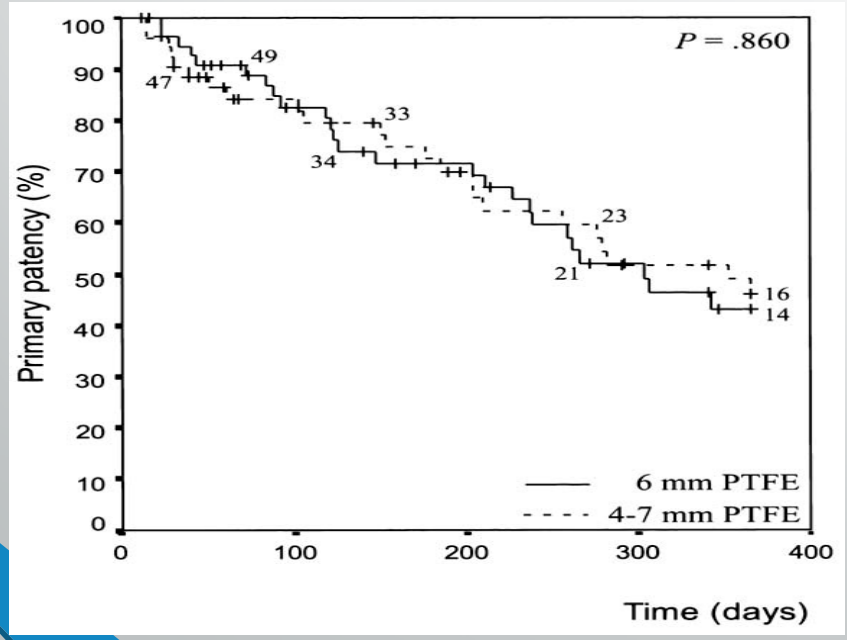
- Grafts with Cuffs
- Tapered Grafts
- Helical or Swirl Grafts/ Spiral grafts

In Vivo vs In Vitro

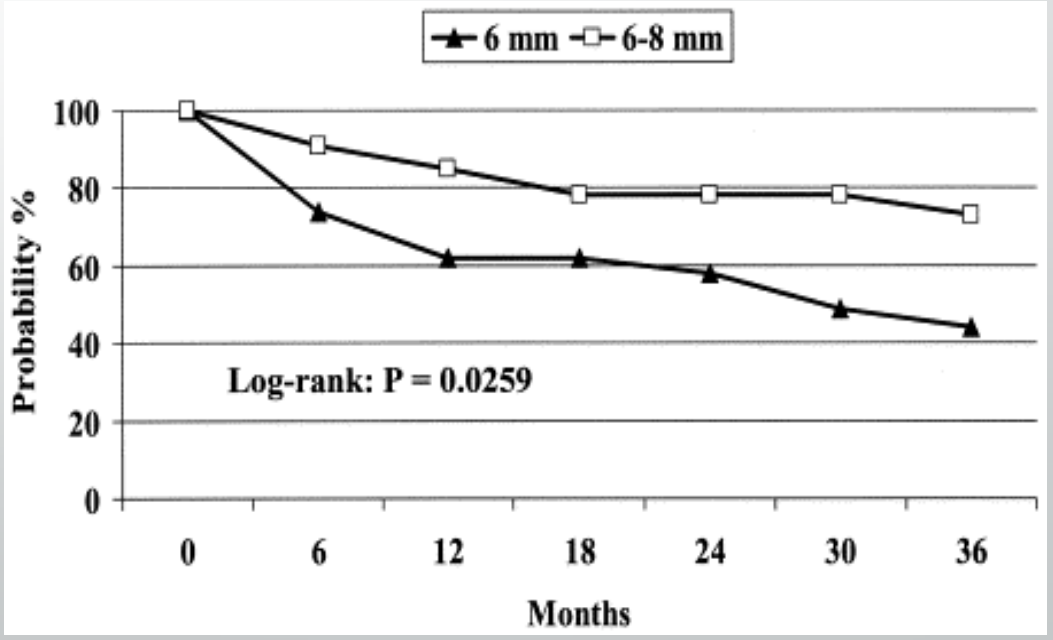
- Grafts with Cuffs at venous end in vitro had lower WSS and homogenous flow pattern however human data is sparse and only a few studies demonstrate improved patency rates with cuffs vs straight grafts

Primary patency of Tapered Grafts

Dammers JVS 2003



Polo, JVS 2004



Graft Geometry and flow modulation

- Swirl graft by Veryan- excellent animal studies demonstrating reduced NIH but human studies did not confirm these results
- Helical Grafts- Excellent animal studies- some human studies do show some moderate improvement in patency rates, however larger studies will be needed to confirm improvement

Graft Coatings

- Heparin
- Paclitaxel/ Sirolimus
- Phosphoryl choline
- PRT-201 (Recombinant human type 1 pancreatic elastase

Prevent Thrombosis

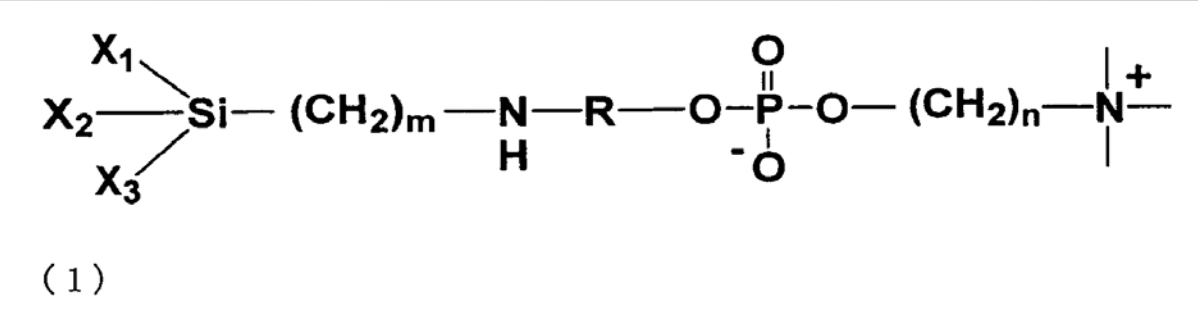
- Heparin coated ePTFE graft by WL Gore
  - One randomized trial and one retrospective trial looking at the effects of this drug on AV access patency
  - Shemesh randomized 160 patients with 80 to control ePTFE graft and 80 to heparin bonded grafts
    - They found that the heparin bonded grafts had fewer 1 month thrombosis than the control grafts but was not statistically significant
    - The advantage of decreasing thrombosis was noted through 6 months but the cumulative thrombosis rate loss its significance.
    - Zea reported on retrospective trial of 71 patients, 32 who had heparin bonded and 39 control. Could not demonstrate any benefit to the use of heparin bonded in functional patency and in fact their reintervention rate was higher in heparin bonding than control

Graft Coatings

- Paclitaxel
- Cytostatic effect on proliferating cells with inhibition of NIH
  - Coating –Dipping method and luminal coating results in high systemic levels
  - Wraps-No high systemic levels but local site complications noted
  - Nanoparticles-no in vivo data but in vitro data demonstrates longer release of drug

Graft coatings

- Sirolimus wrap
- Decreases NIH in vivo models
- Perivascular implant demonstrates in small group of patient very safe and improved outcomes of primary patency rates of grafts.



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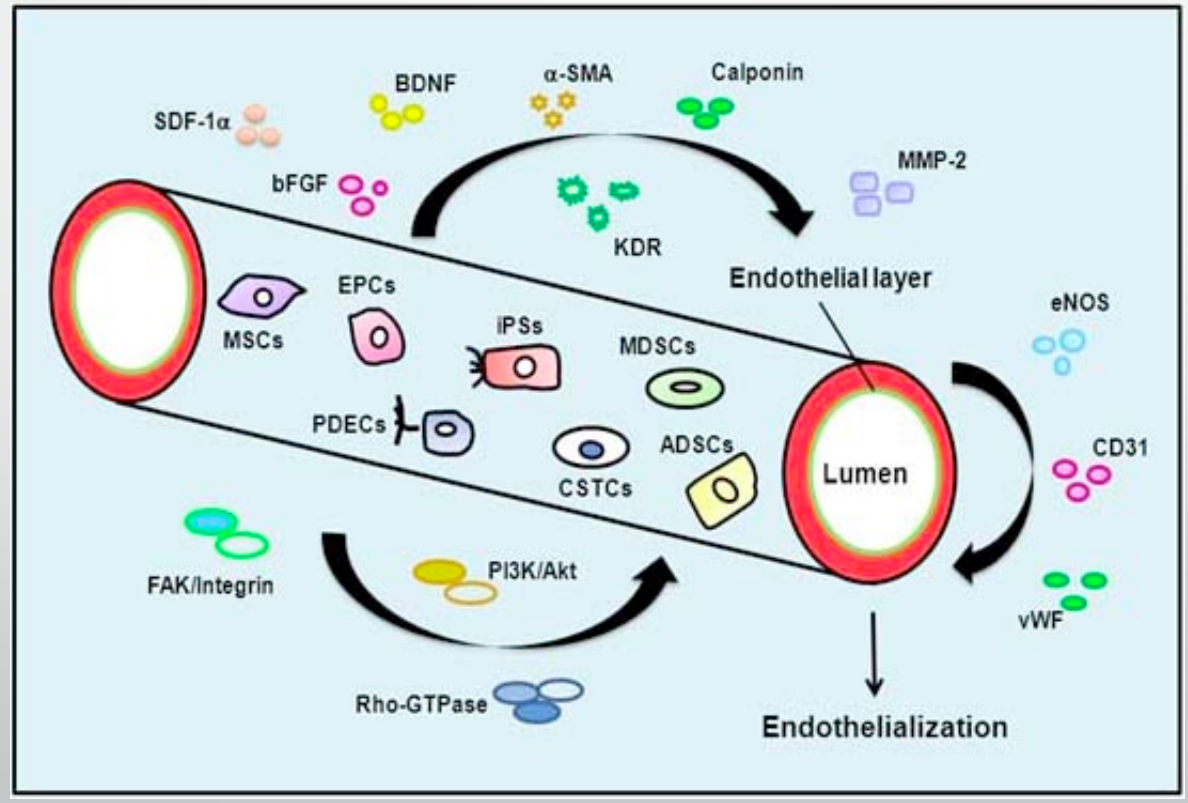
Reducing intimal hyperplasia

- Most of the exciting work is in this field!
  - Paclitaxel coating by local delivery at 3 mm at either the venous end and arterial end.
    - Porcine model-Significant reduction in local delivery grafts to standard in development of intimal hyperplasia
    - The reduction in intimal hyperplasia was similar to grafts fully coated with Paclitaxel
    - This is a significant finding and could alleviate the toxic results from higher concentrations of this drug

Graft Coatings

- Phosphoryl choline
  - Phospholipid on the outer surface of red blood cells
  - Part of platelet activating factor
  - In Vivo study demonstrates decrease in thrombogenicity and NIH formation

Need for Endothelial lining for production of vasoactive properties



Reendothelialization of Grafts

- Graft surface technology
  - Chemical Surface modification-Homogenously distributed chemical reactions to increase hydrophilic properties and increase cell adhesion
  - Microtopography
  - Nano topography
- Tissue Engineering

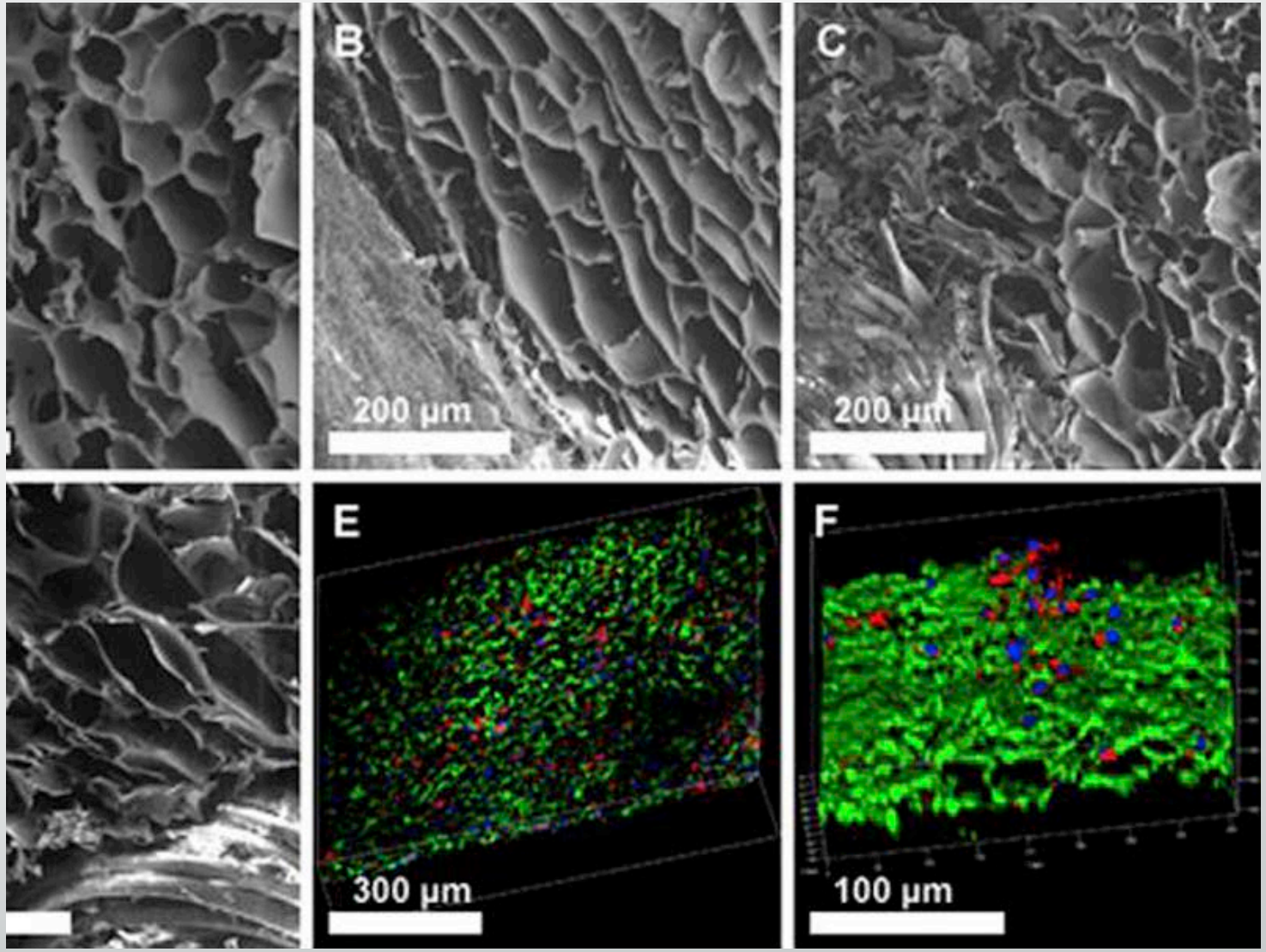
Reducing Intimal Hyperplasia

- Use of a Polyethylene terephthalate fabric (PET) using a biodegradable material such as poly glycolic acid offers different techniques to graft materials.
  - Huynh developed a hybrid graft using this technique of elect spun ePET graft. They delivered small amounts of RNA (siRNA) and other modulator of the anastomotic response and antithrombotics . Human aortic endothelial cells were also incorporated and allowed for proliferation in 7 days. The cryogen was stable after 8 weeks.
  - This concept allows for flexibility in creating prosthetic grafts adaptable to evolving strategies

Graft Analysis

- Scanning EM at 8 weeks
- E: Cell incorporation in hybrid ePET graft
- F: Incorporation in hybrid Knitted ePET graft

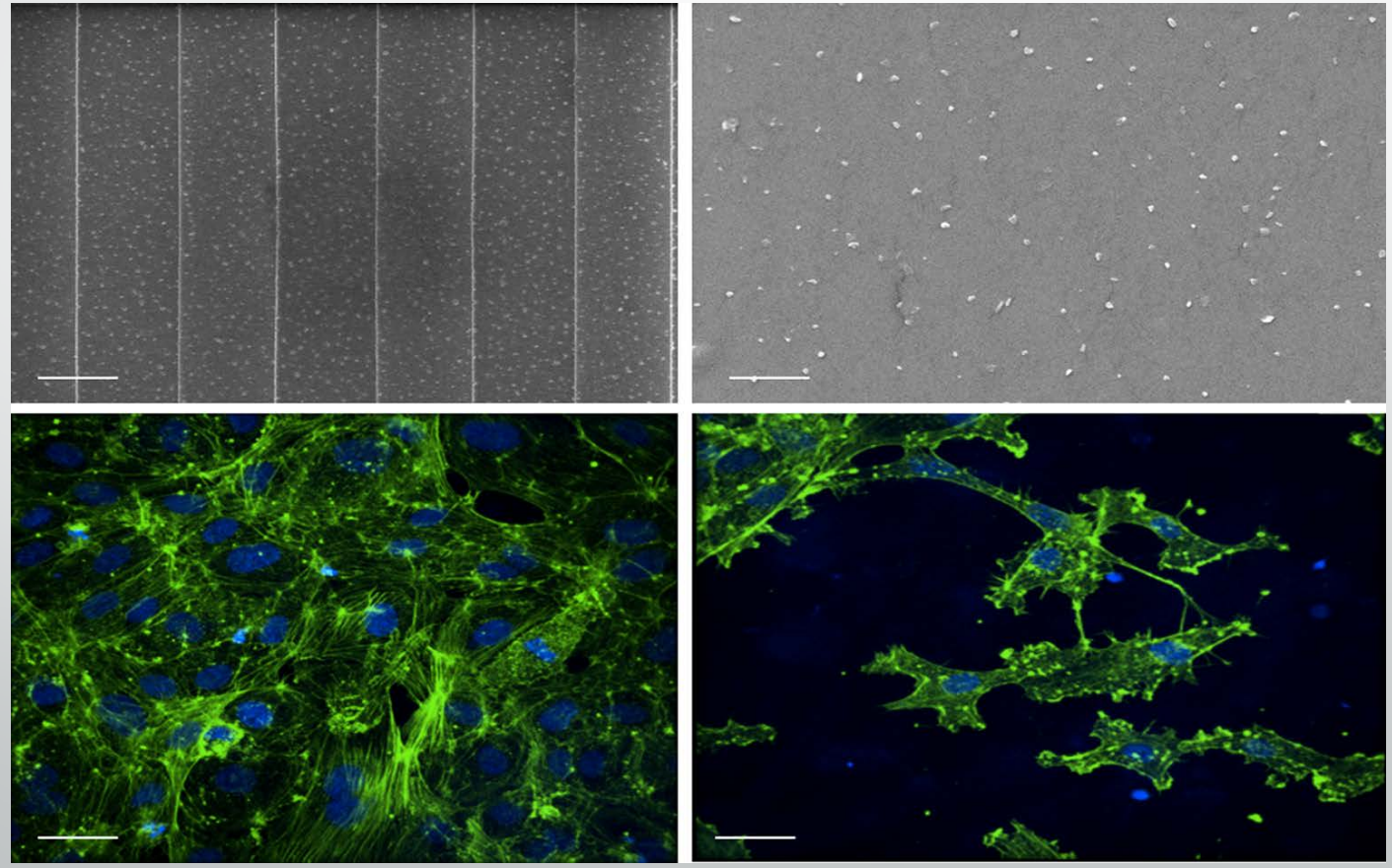
- Cell nuclei are blue



Luminal Surface Engineering

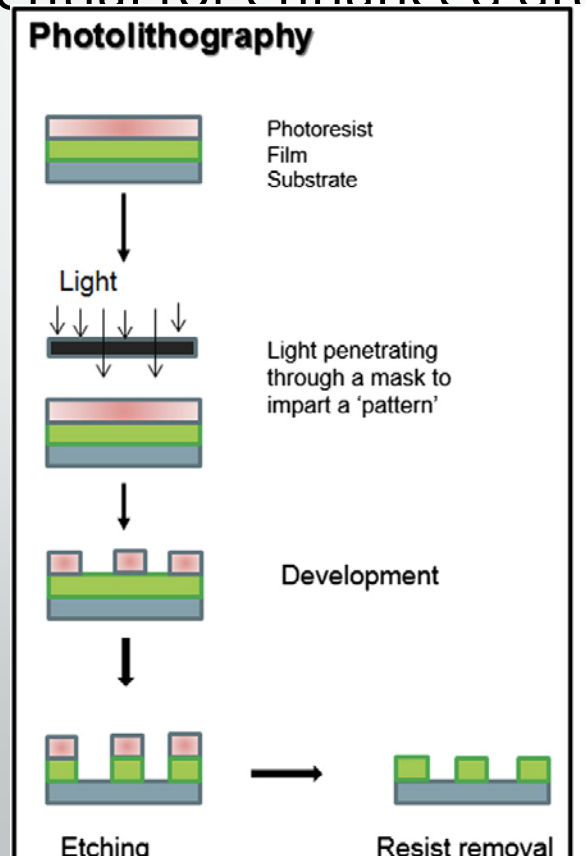
- Micro and Nanopatterning
- A specific patterns of grooves and ridges
- Facilitates adhesions of cells to the graft surfaces

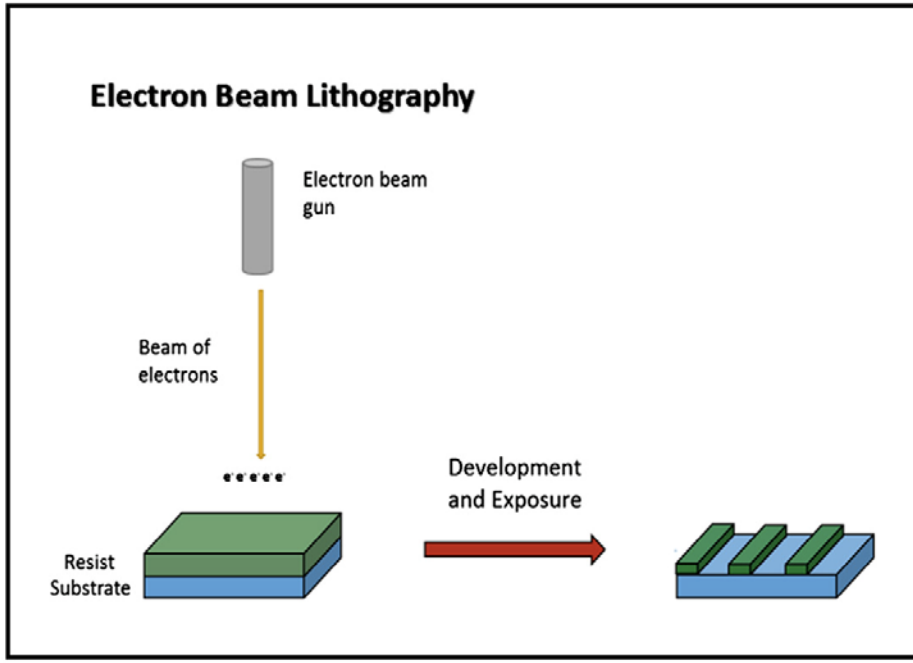
Luminal Surface Engineering



Reducing intimal hyperplasia

- Lastly the use of Nanotopgraphy and plasma treatment, redesigning surfaces of grafts allows for better endothelialization of the grafts and potential for enhanced graft survival.

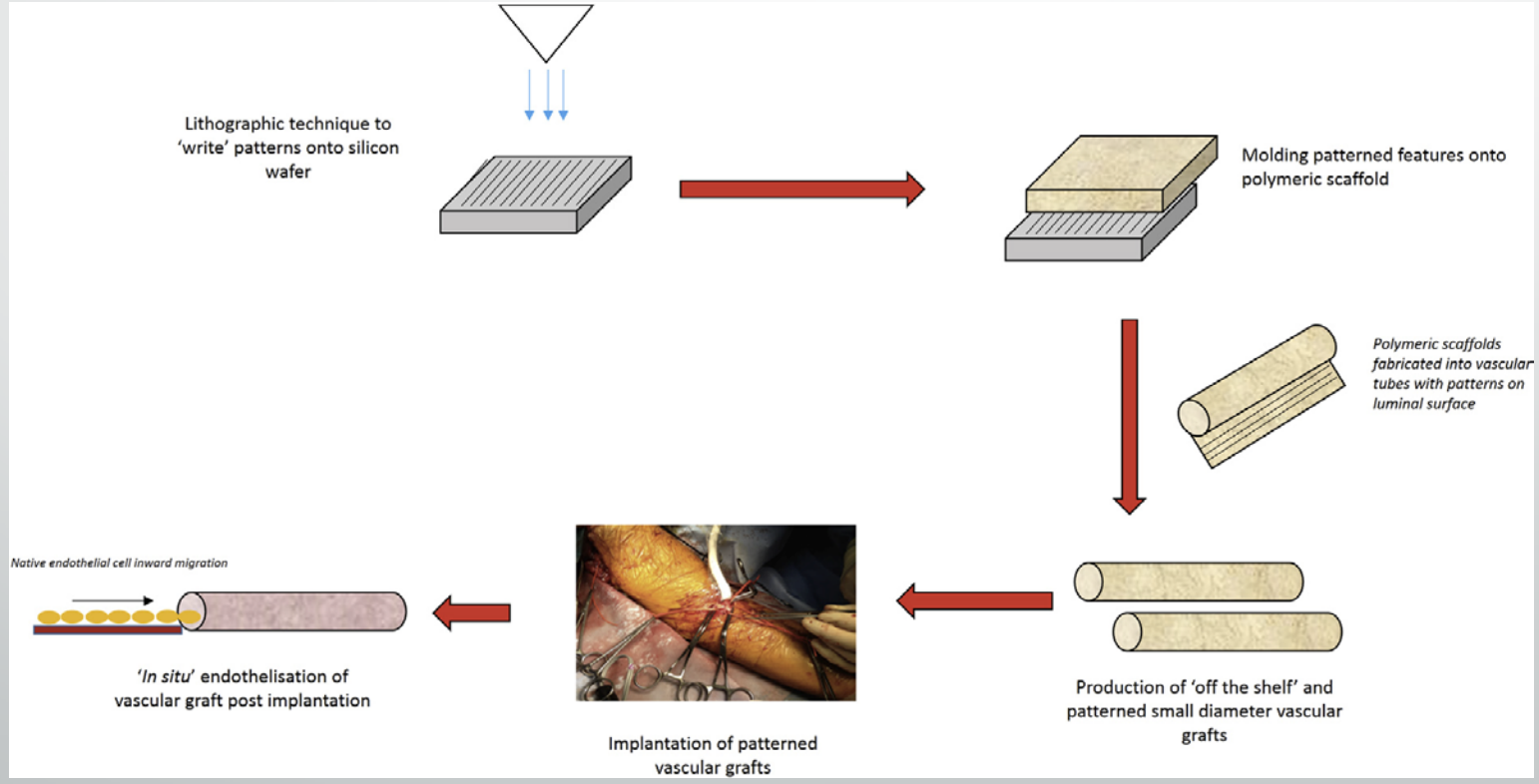




Luminal Surface Engineering

- Photolithography
- Electron Beam Lithography
- Soft Lithography
- Electrospinning

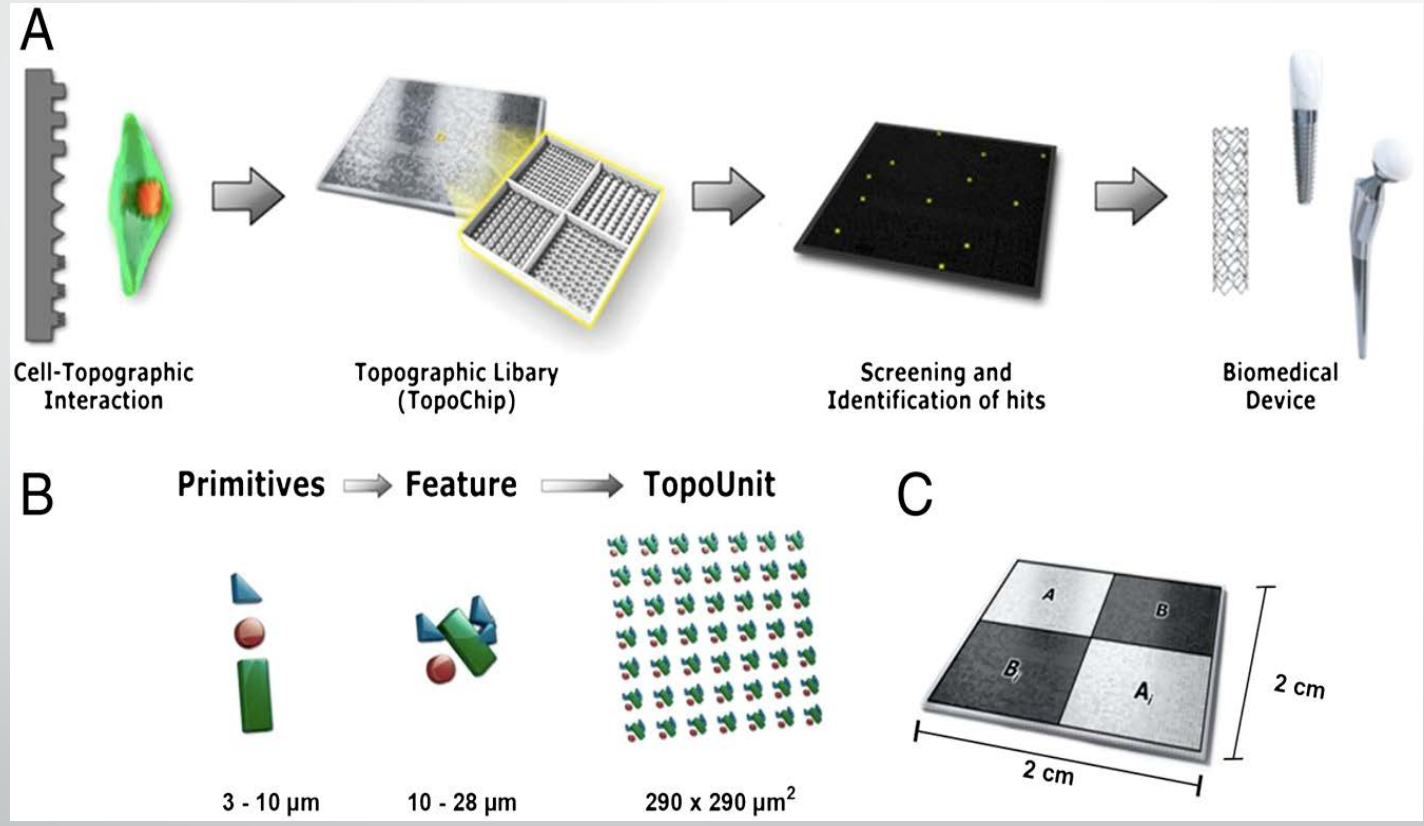
Luminal Surface Engineering



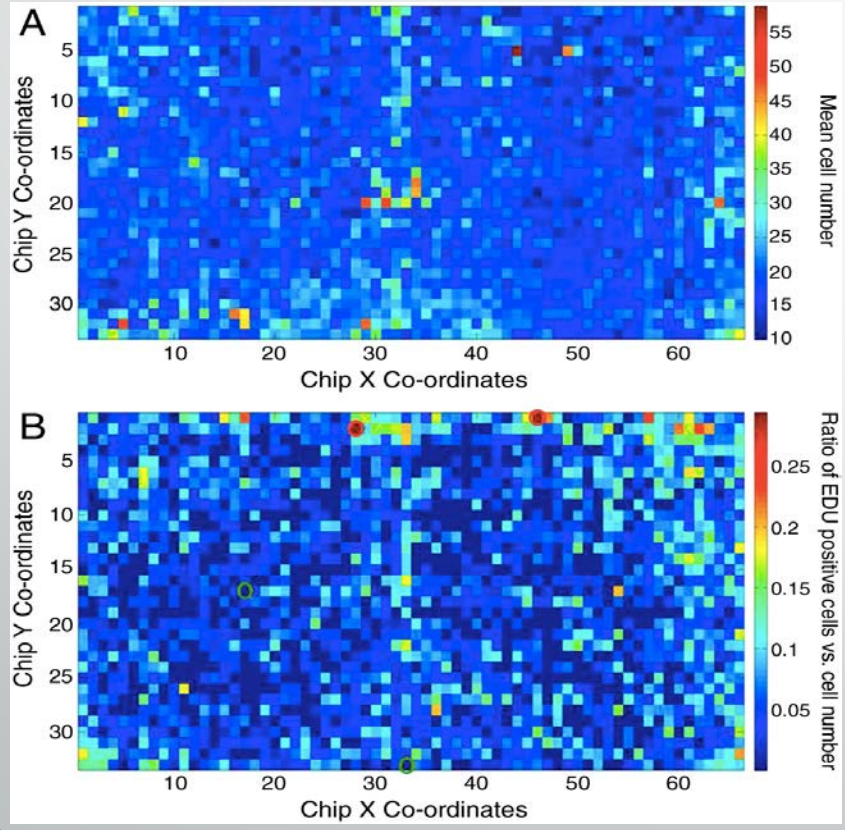
Luminal Surface Engineering

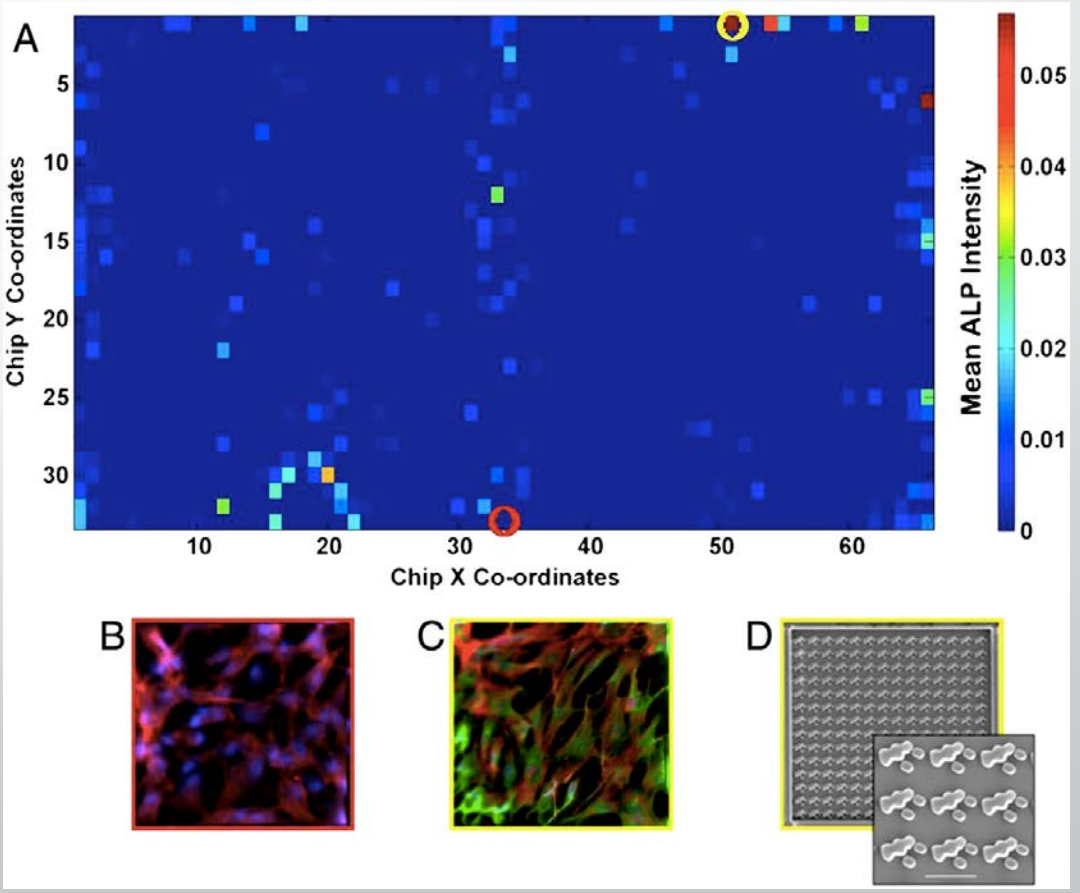
- “Top Chip” Technology

Top Chip Technology



Top
Chip Technology





Reduce Infection

The use of electro spun biodegradable Nano-fibers offers potential for the access community

Using Vancomycin Nano-fiber loaded into a graft has demonstrated high concentrations of the drug for over 8 months in Rabbit Model.

This new graft may serve our dialysis patients by reducing the infection rate at cannulation site

Tissue Engineering of Vascular grafts

- Studies underway to determine improvement in outcomes with these grafts
- Three entities involved in vascular graft designs
- Exciting time to see improvements in outcomes for grafts

Summary

- Over 40 years, change has been slow. Materials, geometry, coatings and now endoluminal surfacing may provide significant improvement in outcomes of prosthetic grafts