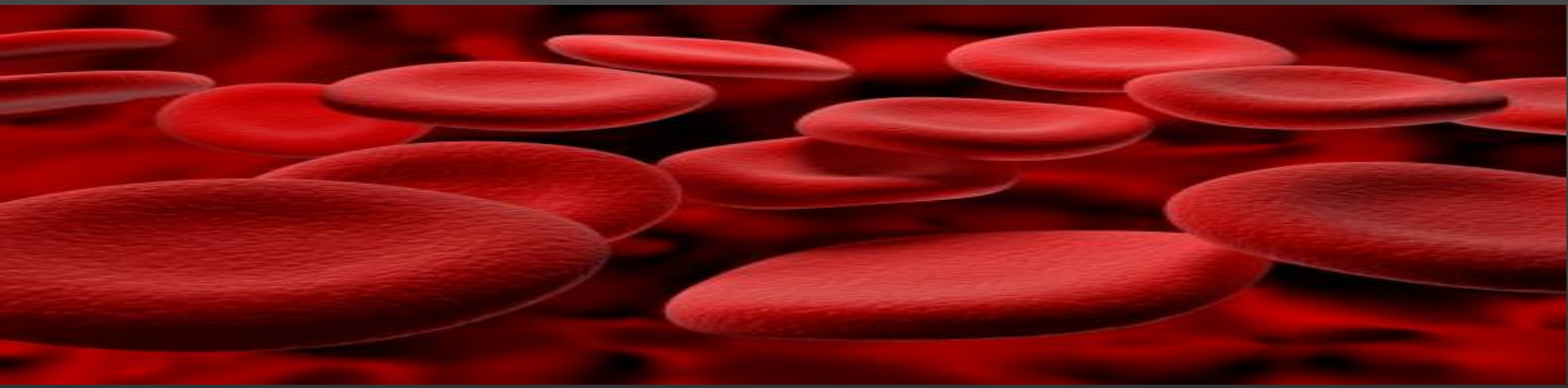
Team Aggregation Domination Oral Report 3



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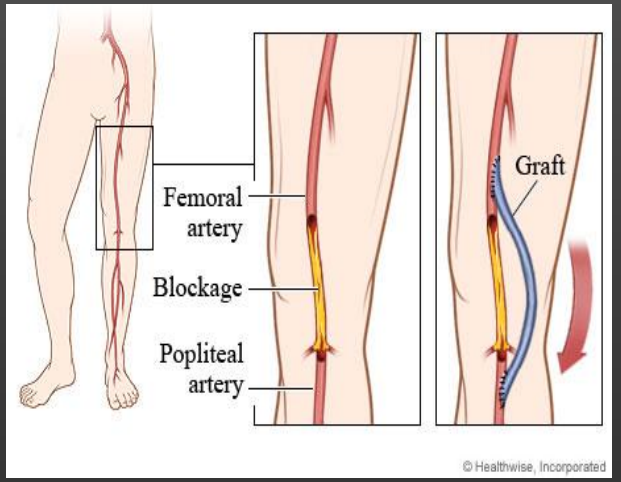
Background

Vascular bypass graft failure rates can be as high as 43% depending on the type of operation.

This failure is thought to be caused by the inflammatory response induced from trauma during transplantation.

Scientists have developed an map kinase inhibitor that moderates endothelial cellular processes such as proliferation, stress response, and apoptosis.

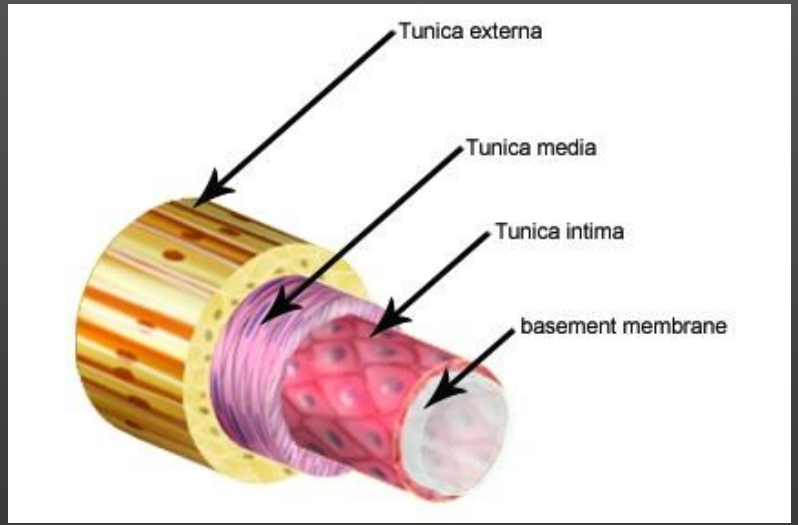
Vascular bypass graft patency has been shown to improve with treatment using this MK2 inhibitor.



Myhealth.albert.ca

Problem Statement

- Permeation of this drug is limited by vascular tissue's inherent diffusional barriers.
- The target tissues for this drug are the tunica intima and tunica media.



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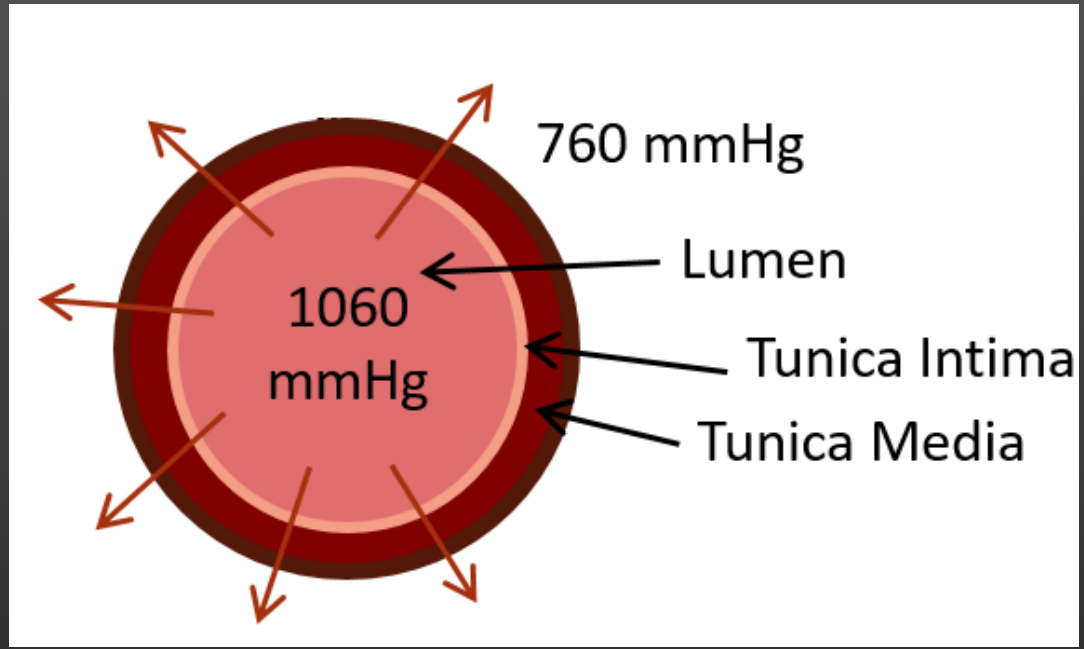
We are developing a pressurized device that will deliver prophylactic drugs into the target tissue of the vessel used for vascular bypass graft transplant

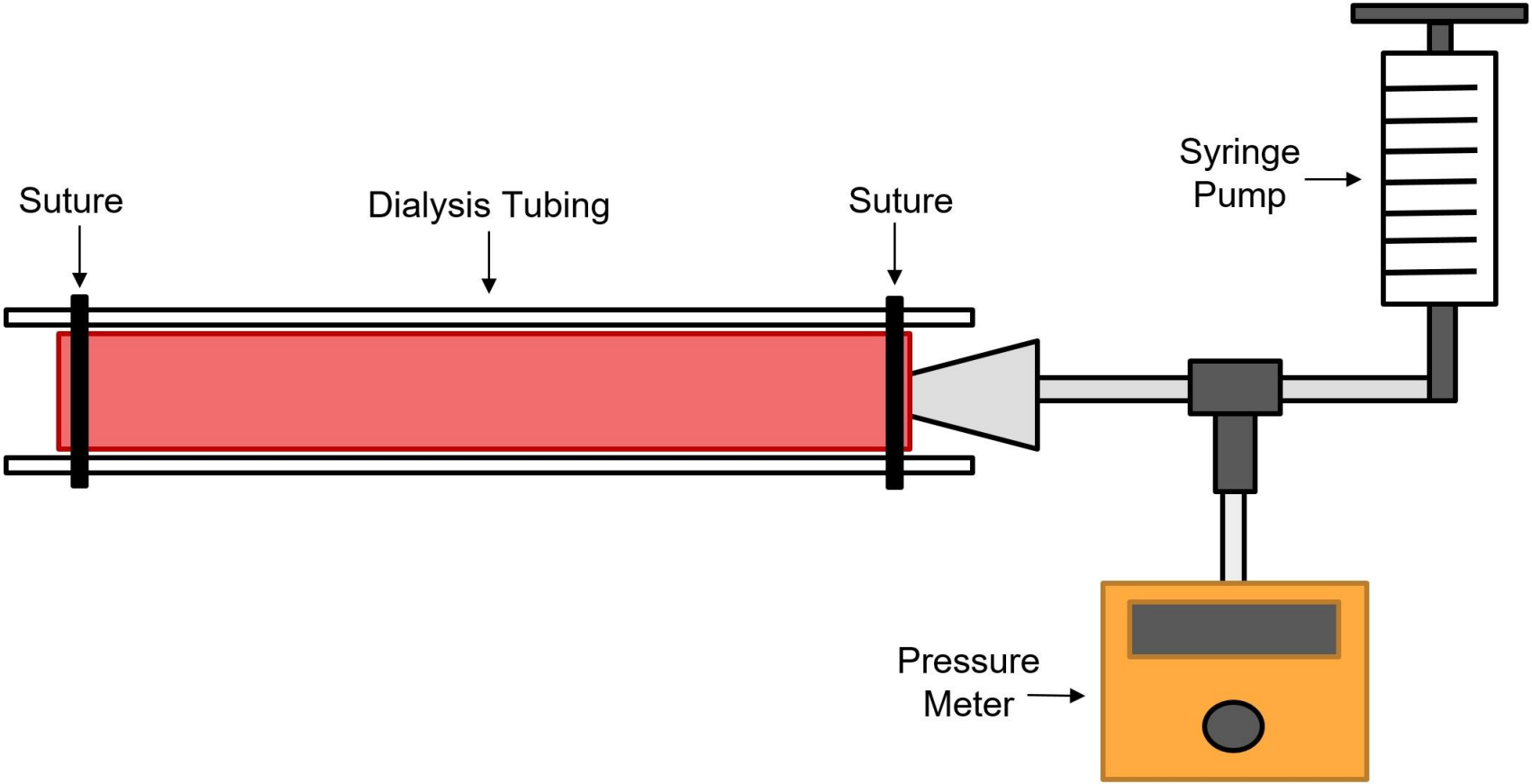
Needs Assessment

- Membrane needs to maintain stiffness to reduce circumferential distension of the vessel
- Membrane will be semipermeable to the MK2 inhibitor
- MK2 inhibitor should be delivered in a timely manner
- Easily integrated into current operating room technologies

Mechanism

- Pressure creates gradient from lumen to exterior of the vessel
- Convective circumferential flow of the drug solution into the target tissue
- Should result in a more effective mode of delivery than current method of treatment

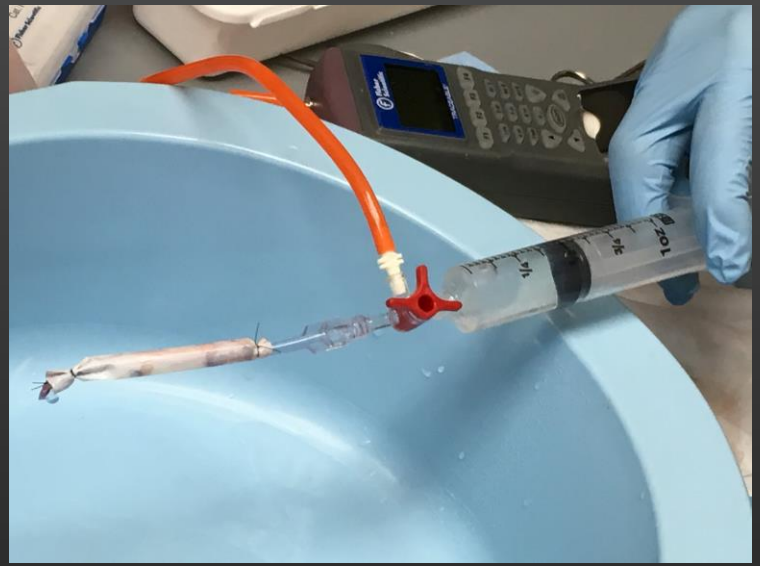



Suture
Dialysis Tubing
Suture
Syringe
Pump
Pressure
Meter

Previous Work

Initial Vein Pressurization Protocol

1. Suture vein to cannula
2. Use guidewire manipulate vein into dialysis tubing
3. Suture both ends until sealed
4. Assemble three way stopcock with vein cannula, pressure meter and filled syringe
5. Pressurize to desired level



Previous Work

Take-away :

- Can reach desired pressures of 132, 300, 600 mmHg.
- Multiple sutures necessary to completely seal the dialysis tubing.
- Veins are not sturdy enough to push through dialysis tubing alone.

Moving Forward :

- A guidewire is a necessary component to our design.
- Dialysis tubing clamps may be necessary to completely seal the tubing.
- Determine if dialysis tubing is providing enough support to prevent damage.

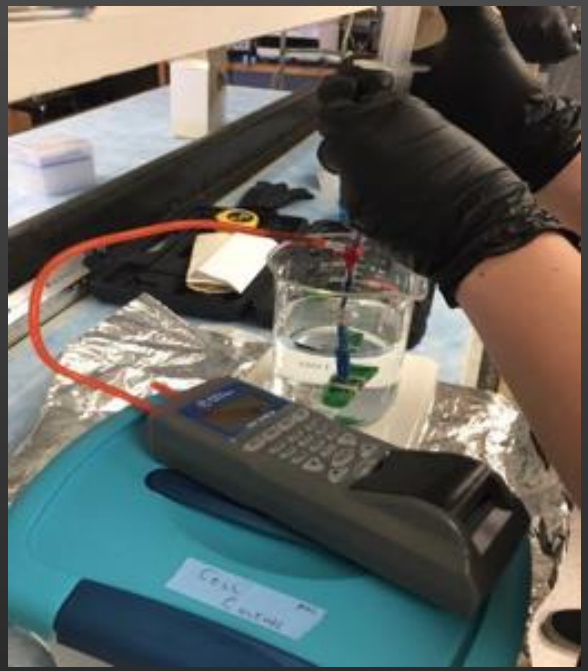
Previous Work

Dialysis Tubing Flow Test: Is Tubing Limiting the Pressure

Goal: Compare the hydraulic conductivity of veins to the dialysis tubing.

Passed a dye solution through the 100 kDa dialysis tubing and measured rate of escape.

From data, calculate hydraulic conductivity of dialysis tubing and compare to studies of vein hydraulic conductivity.

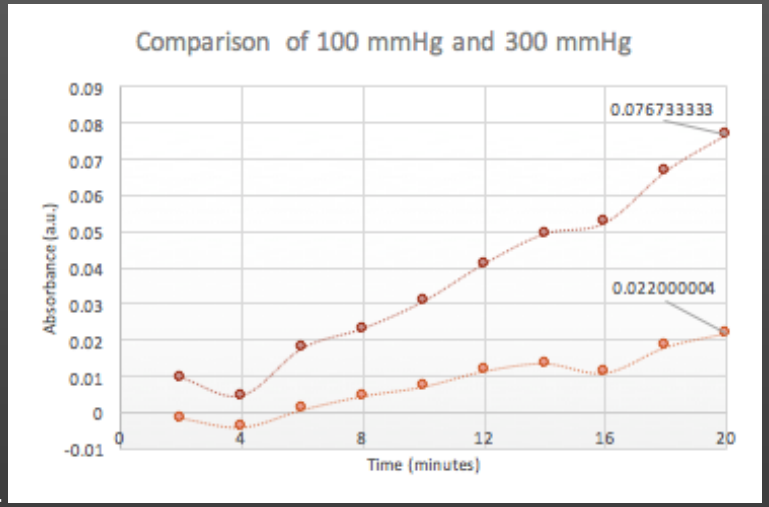


Previous Work

Conclusions:

Vena cava were tested hydraulic conductivity of 1.23*10^-7 (cm/(s*mmHg)) (Vargas 1986) meaning approximately 80% of the pressure drop is across the vein wall.

Additionally, the sutures do not leak up to pressures of 300 mmHg.



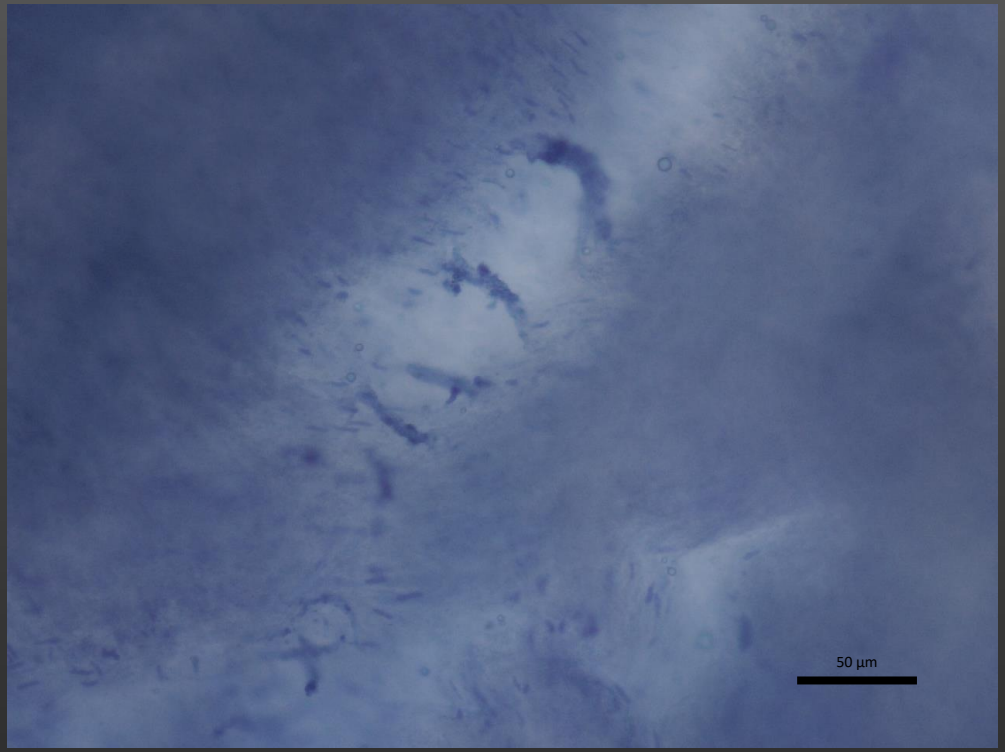
Red: 300 mmHg, Orange: 100 mmHg

	100 mmHg	300 mmHg
Hydraulic Conductivity (cm/(s*mmHg)	7.16E-07	4.70E-07

Previous Work

Positive Control for Tissue Damage Assessment

- Tissue damage can be qualitatively assessed using this method
- The tissue will be evaluated on the following grounds:
  - Cobblestone morphology
  - Cuboidal contact
  - No visualized basement membrane



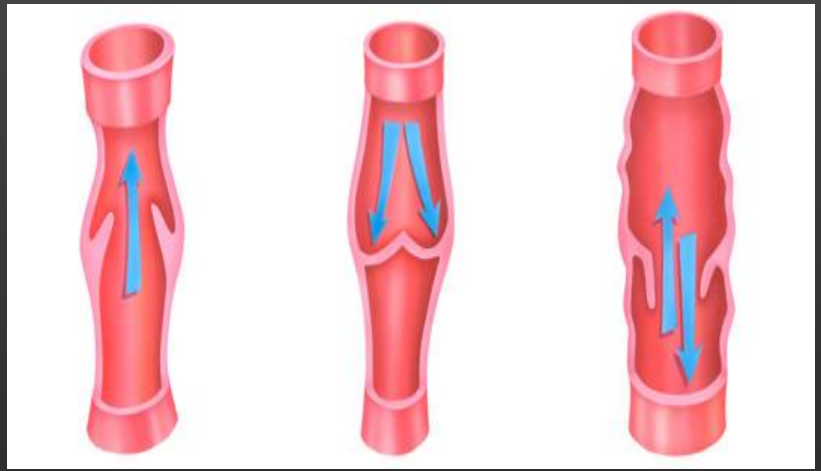
Weekly Goals

- Run a drug permeation experiment at 132 mmHG, 300 mmHg, and 600 mmHg pressures to determine a working flow for future tests
- Determine which pressure results in significant tissue penetration depth

Permeation Experiment - Background

- During a vascular bypass procedure, doctors distend the vein in order to prevent vasospasms as well as to blow out the valves that are inherent to vein structure.
- The vein we acquired this week had already been distended.
- We ran our flow experiment anyway to determine if we could get any tissue penetration at a safe pressure. We will use these results to set up a flow experiment with porcine carotid arteries.

Proximal End



Veinsandlasercenterofnj.com

Distal End

Permeation Experiment - Procedure

- Important Note: two veins were used from two different patients (one was split for control groups, others were used for pressurized trials)

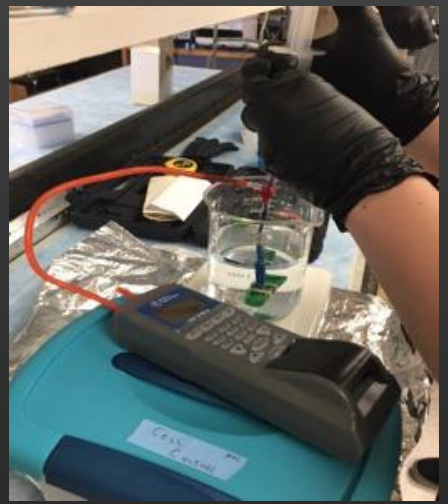
- Began with two different control groups

1. Untreated Negative Control
   - section off a small piece of vessel
   - add OCT compound to square mold
   - submerge vessel into the OCT (no bubbles)
   - set on top of dry ice and store

2. Pressure Control
   - tied off vessel and inserted cannula
   - added the FITC-BSA solution into the middle of the tied off vessel
   - sit for 10 minutes
   - washed and segmented vessel (from middle)
   - set up for cryosectioning

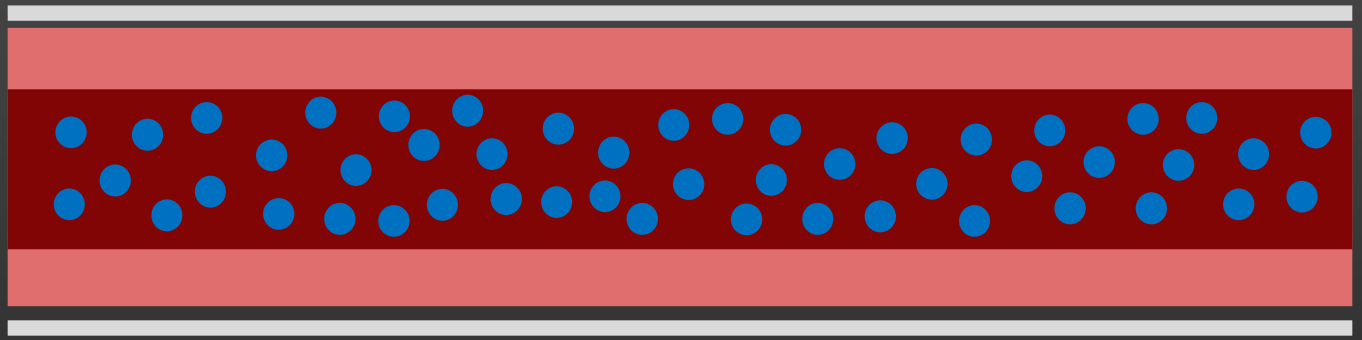
Permeation Experiment - Procedure

3. Pressurization Trials
- tied a wire to the end of the vein and thread it through tubing
- cut the tubing and veins into three sections (one for each pressure)
- take one segment and attach it onto the cannula and assemble
- pressurize with the FITC-BSA solution until full
  (to ensure no leakage)
- pressurize at a constant pressure
  (132 mmHG, 300 mmHg, 600 mmHg)
- after 10 minutes remove the vessel from the device
  and wash with PBS
- section the middle of the vessel
- prepare for cryosectioning



Permeation Experiment - Results

- We were unable to perform cryosectioning and fluorescence microscopy this past week. We are hoping to perform these assessments in the next week or so with our post-doctoral advisor.



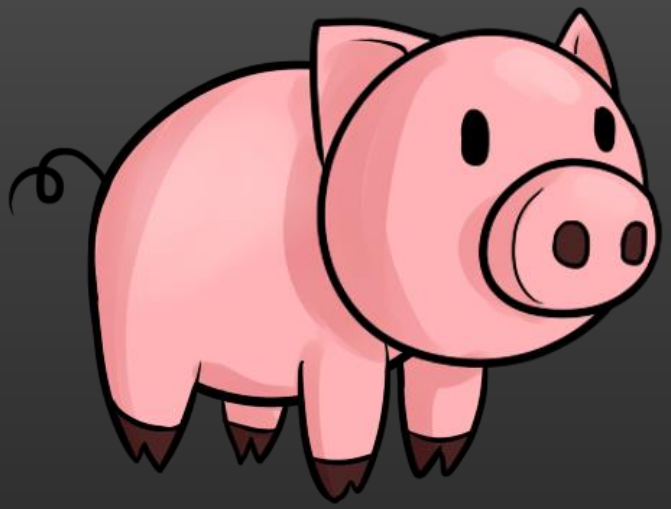
- Expected Results:
  - Deeper permeation from pressurized trials than control
  - Linear relationship between increased pressure and increased permeation

Future Work: Current Issues

Veins from hospital already distended and damaged.

Because of this we aren't consistently able to conduct experiments.

Future Work: Other Vein Sources



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The pig as a model for translational research: overview of porcine animal models at Jichi Medical University (Kobayashi et al. 2012)

Pros:

- Pigs have similar vascular properties to humans.
- Ideal model for studying vascular diseases and ailments.

Cons:

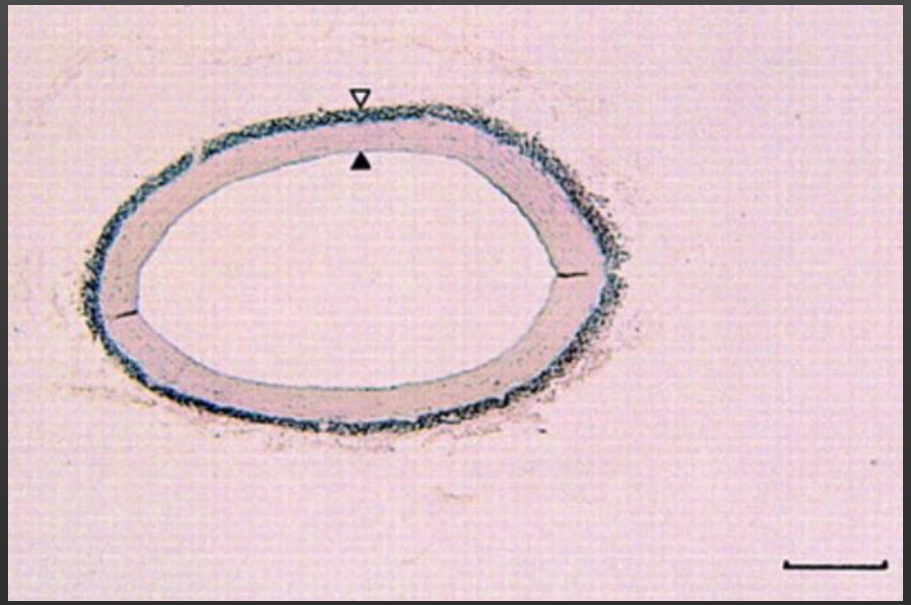
- Expensive to obtain.
- Heavily regulated for research.

Future Work: Pig Model

Comparison of Saphenous Veins:

From Seidel 2005, the average size of a human saphenous vein is approximately 4mm in diameter.

From Izzat 1996, the average size of a pig saphenous vein is also approximately 4mm in diameter.



Future Work: Experiments

1) Drug Permeation -
   With the pig model we can more easily test drug delivery at multiple pressures as well as a control without worrying about vein distension.

2) Tissue Damage Assessment -
   Critical to have non-distended veins for a a tissue damage test to understand how the dialysis tubing is affecting the vein.

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Questions