

# When Innate Immunity Hurts: Implications for Medical Device Failure

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# Learning Targets

- Explain innate immunity/inflammatory response
- Relate phagocytosis to the inflammatory response
- Explain how the inflammatory response is regulated
- Propose mechanisms to inhibit the immune response

# Immunity

## Outside

## Inside



Physical &  
Chemical Barriers  
(skin & mucus  
membranes)

<http://www.republicmortgage.com/wp-content/uploads/How-To-Keep-Your-Home-Germ-Free.jpg>

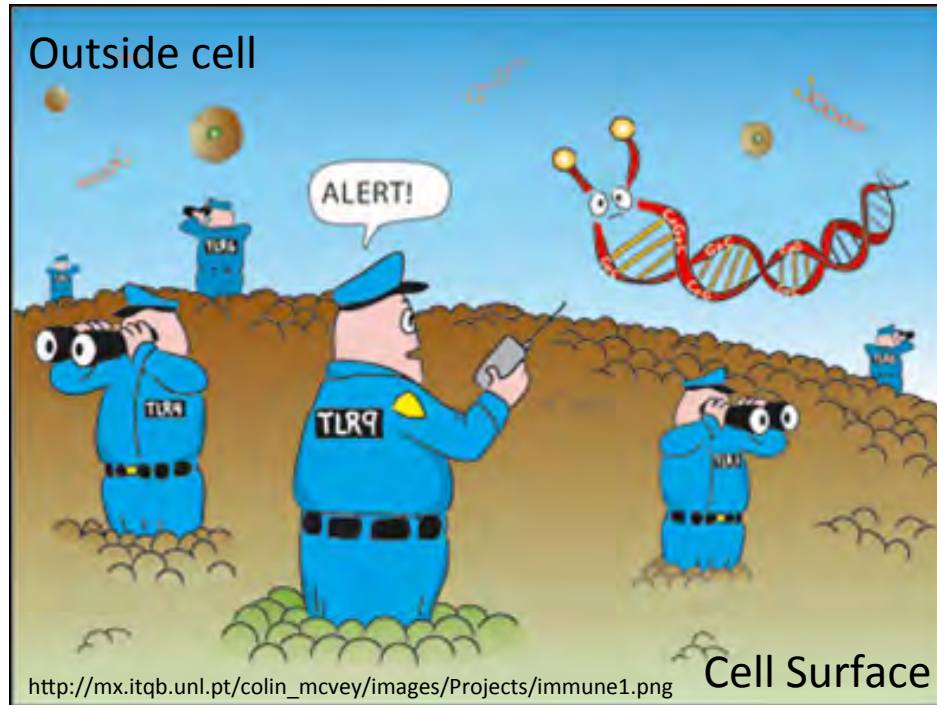
### Innate Immunity

- First line of defense
- Non-specific
- No memory
- Same response to repeat infection

### Adaptive Immunity

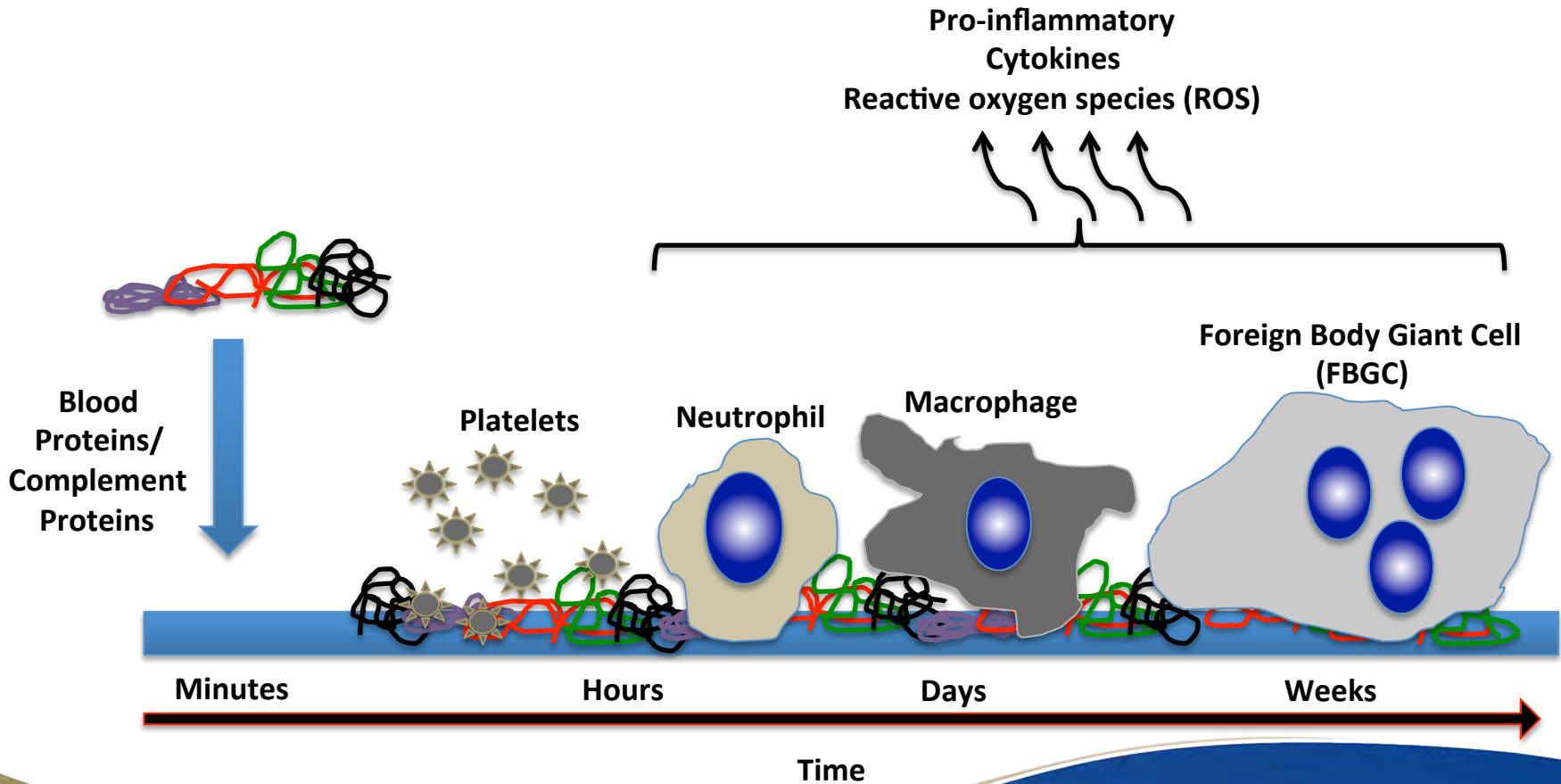
- Max response in days
- Specific
- Memory
- More rapid response to repeat infection

# Innate Immunity

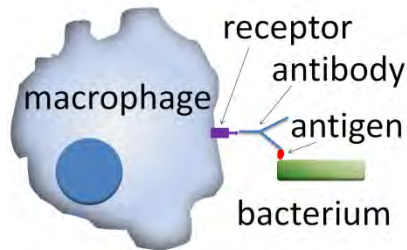
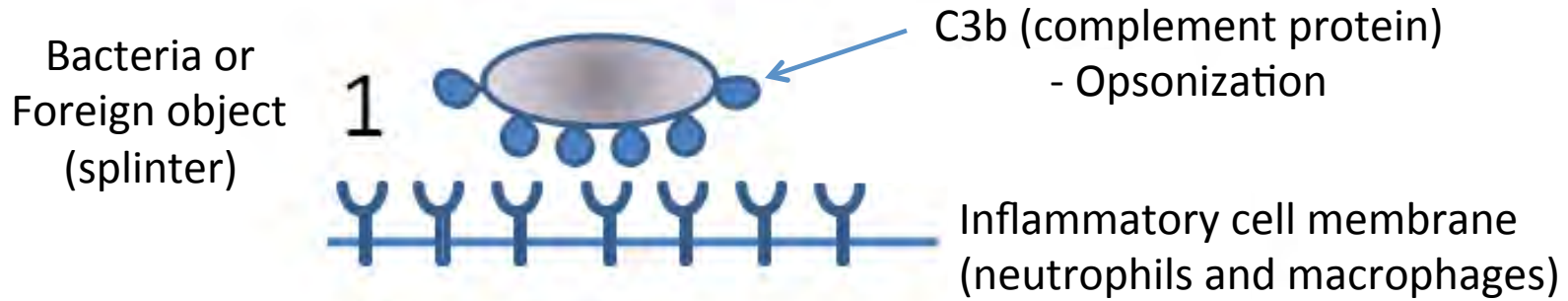


- Inflammation is triggered when innate immune cells detect infection or tissue injury
  - Inflammation is the primary component of innate immunity

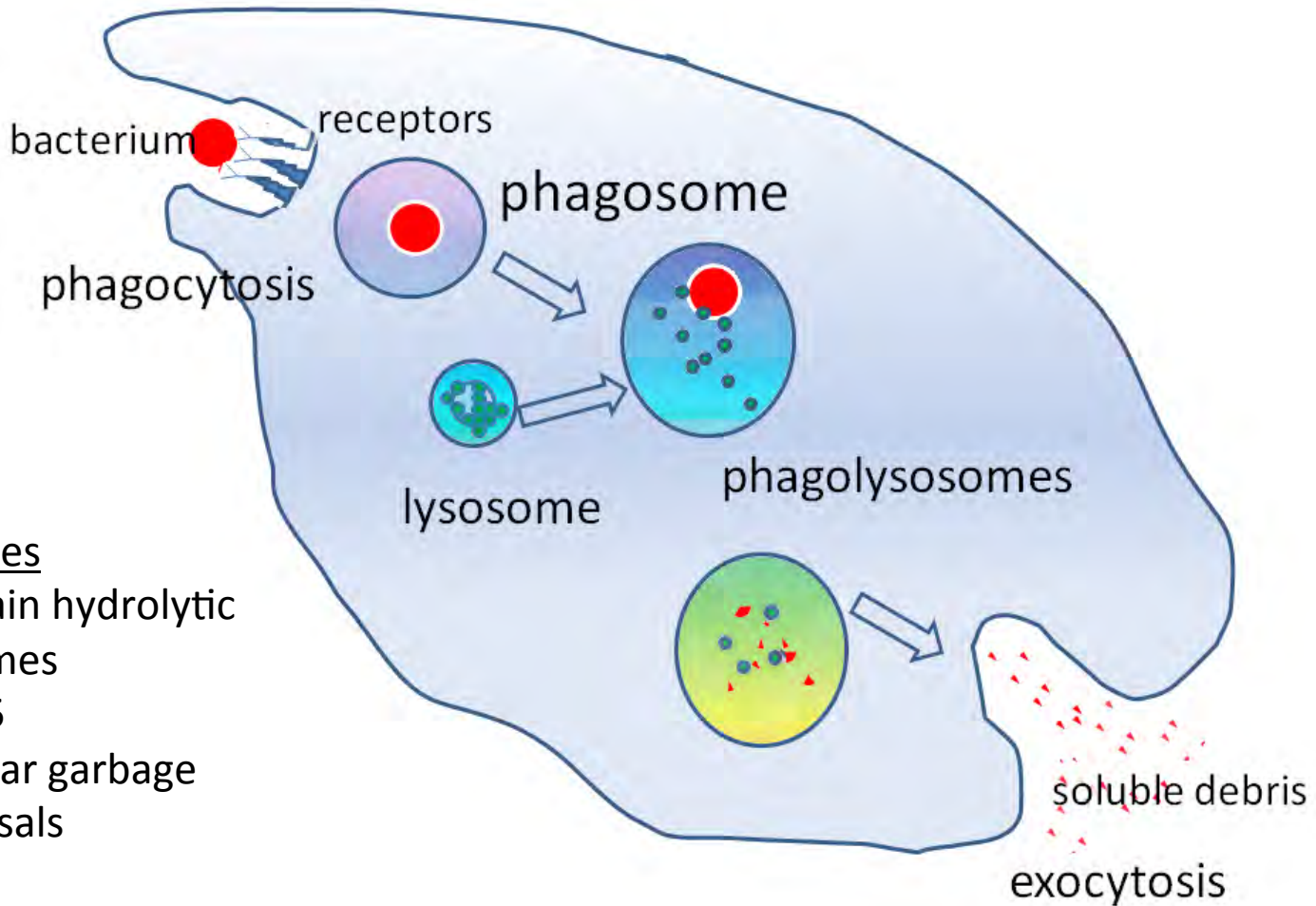
# Inflammatory response



# Phagocytosis



# Phagocytosis



## Lysosomes

- Contain hydrolytic enzymes
- pH ~5
- Cellular garbage disposals

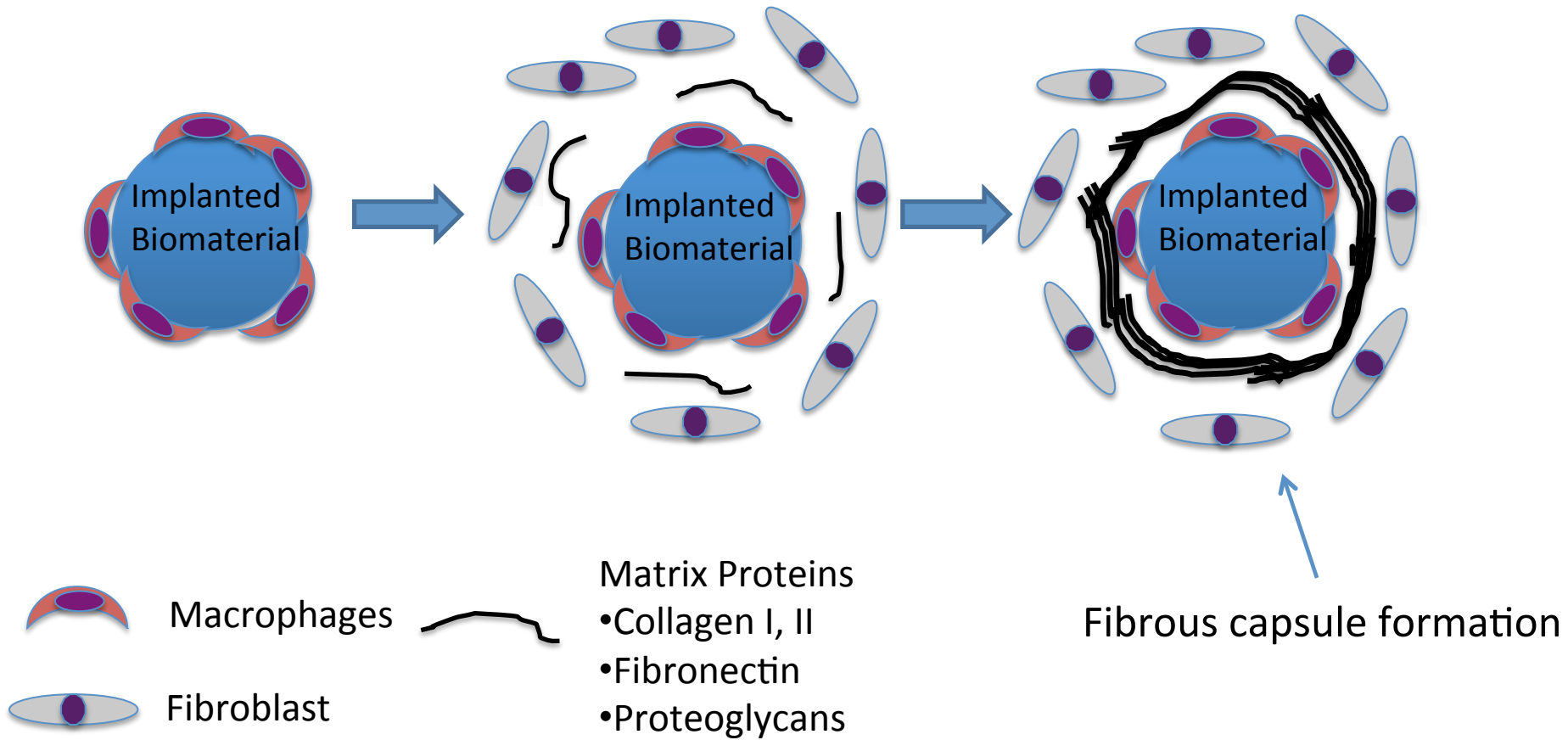
# Phagocytosis - Videos

[http://highered.mheducation.com/sites/0072495855/  
student\\_view0/chapter2/animation\\_\\_phagocytosis.html](http://highered.mheducation.com/sites/0072495855/student_view0/chapter2/animation__phagocytosis.html)

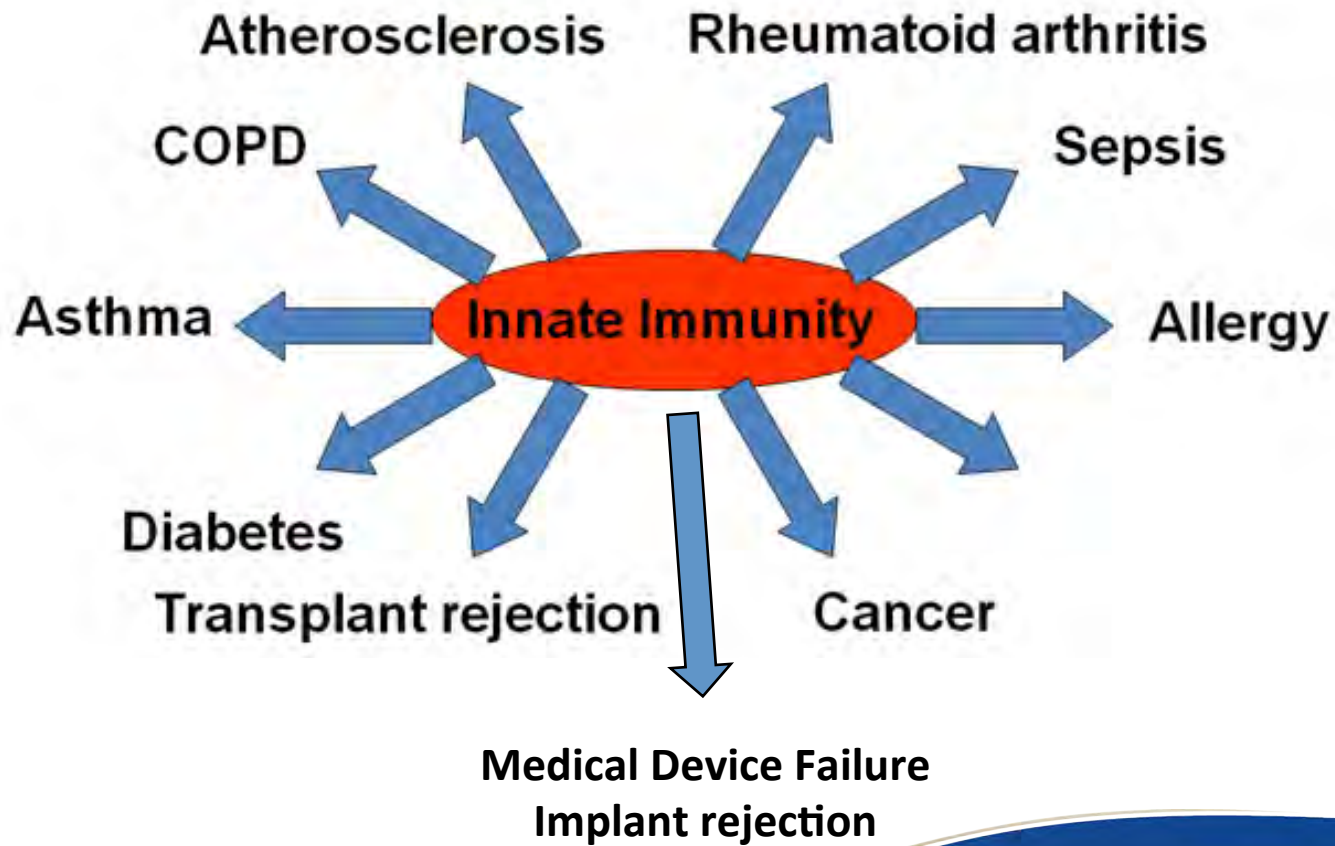
[https://www.youtube.com/watch?v=Z\\_mXDvZQ6dU](https://www.youtube.com/watch?v=Z_mXDvZQ6dU)



# Inflammatory response



# Innate Immunity-Related Diseases



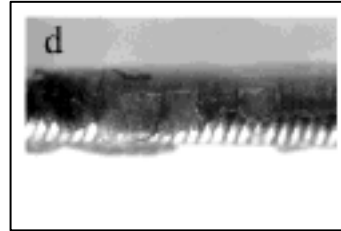
# Think-Pair-Share

- What do you think causes diseases associated with innate immunity?

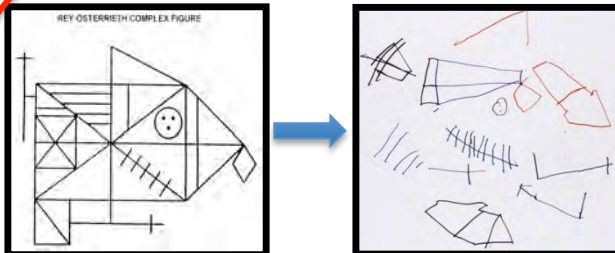
# Issues with Innate Immunity



Restenosis



Cracked pacemaker lead insulation



Post-surgical complications of cardiopulmonary bypass



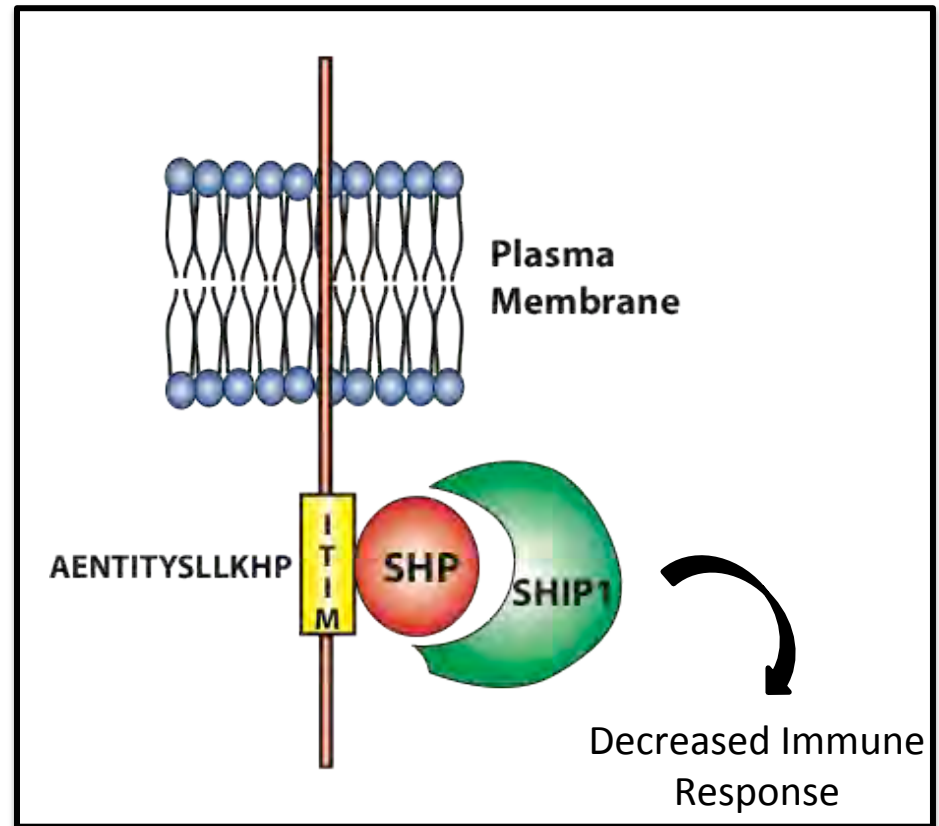
Fig 1. The degenerated St. Jude valve is shown after explantation.

Wiederman et al  
Ann Thorac Surg 2010

Bioprosthetic valve calcification

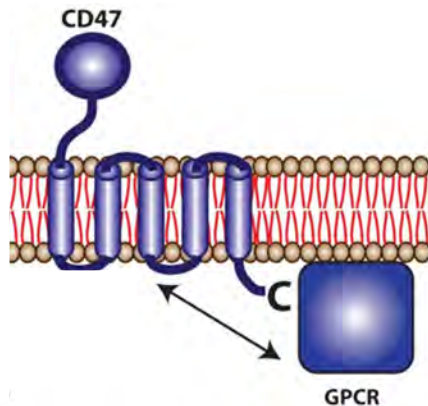
# Regulation of the inflammatory response

- Under homeostatic conditions, response to foreign stimuli closely regulated
- Inhibitory immune cell surface receptors
  - **Signal Regulatory Protein Alpha (SIRP $\alpha$ )**
- Immunoreceptor Tyrosine Inhibitory Motif (ITIM) protein family



# CD47

- Expressed in virtually all cells
- CD47-SIRP $\alpha$  interaction inhibits immune response
- Over-expressed in most cancer cells

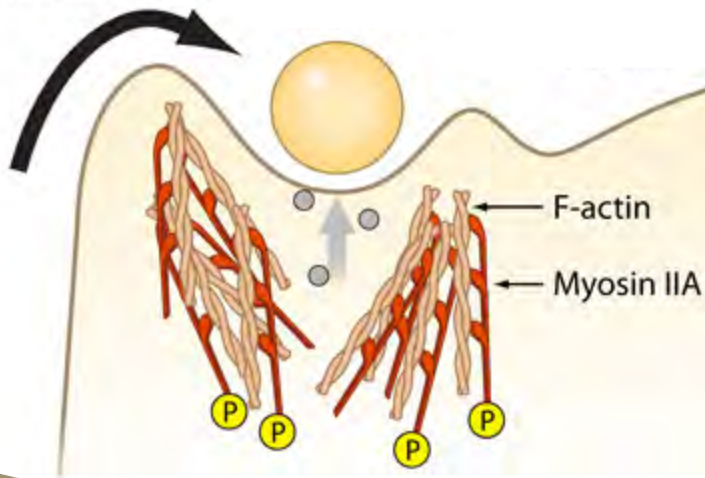


# CD47 – “Don’t Eat Me”

**“Eat me”**

## Phagocytic activation

Cytokine release  
Oxidative burst



# Questions?

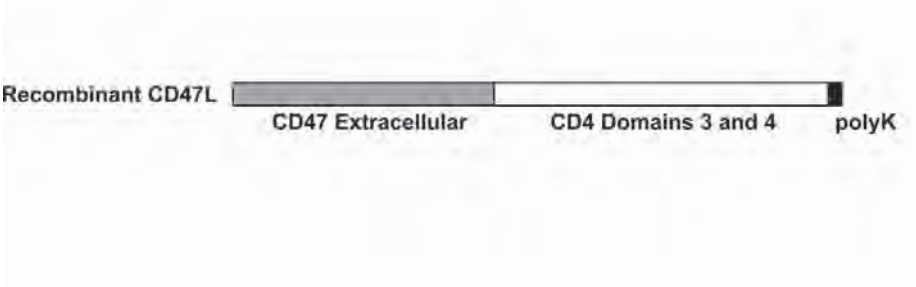


# The use of CD47 as an anti-inflammatory agent on medical polymers

Pacemaker leads, glucose sensors, cardiopulmonary bypass tubing, hemodialysis tubing, & LVAD tubing

# Recombinant CD47 & CD47 Peptide

## Recombinant CD47



Well established

Suited for smaller applications

Contains domains 3 & 4 of rat CD4 as an export sequence

Designed using molecular biology to be secreted by CHO cells

Better suited for larger applications

- Cardiopulmonary bypass tubing
- Hemodialysis tubing
- Left Ventricular Assist Device tubing

More cost effective and modifiable

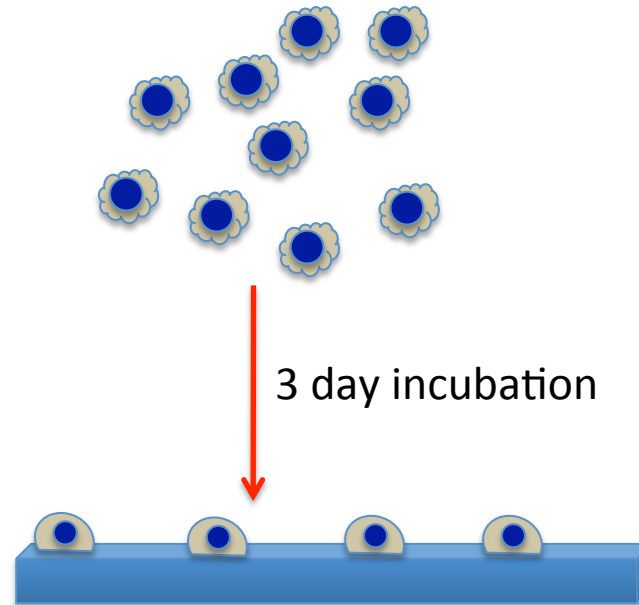
Peptides tend to be more biocompatible

Does CD47 prevent *in vitro* cell attachment?

# *In vitro* assay

## Attachment Assay

THP-1 = human  
monocyte-derived  
macrophage cell line

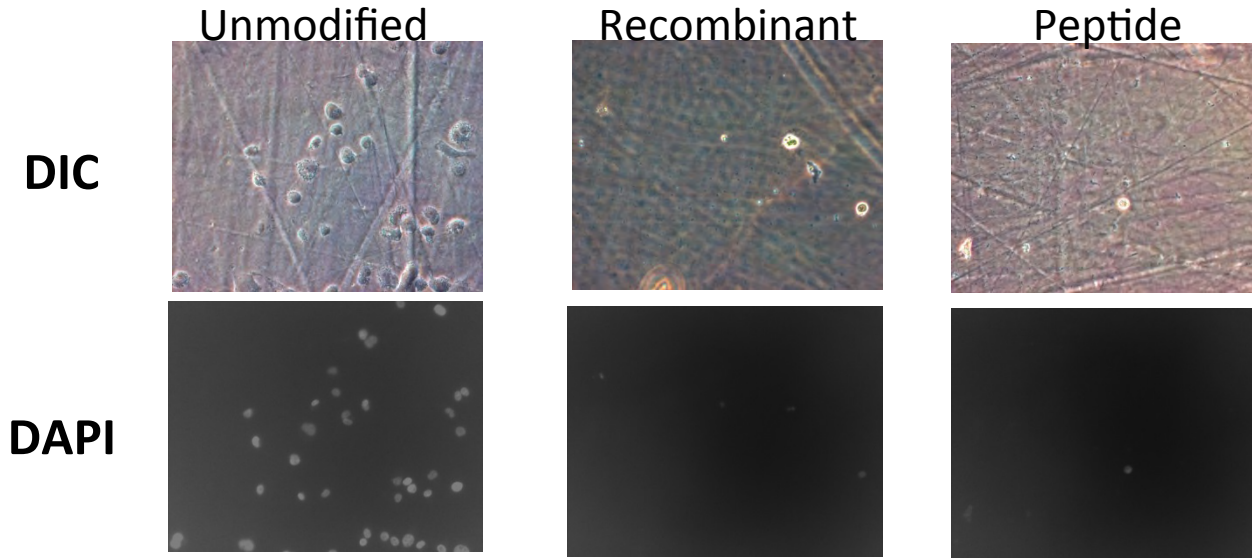


Wash with PBS  
Fix cells  
Stain with DAPI  
Count adhered Cells

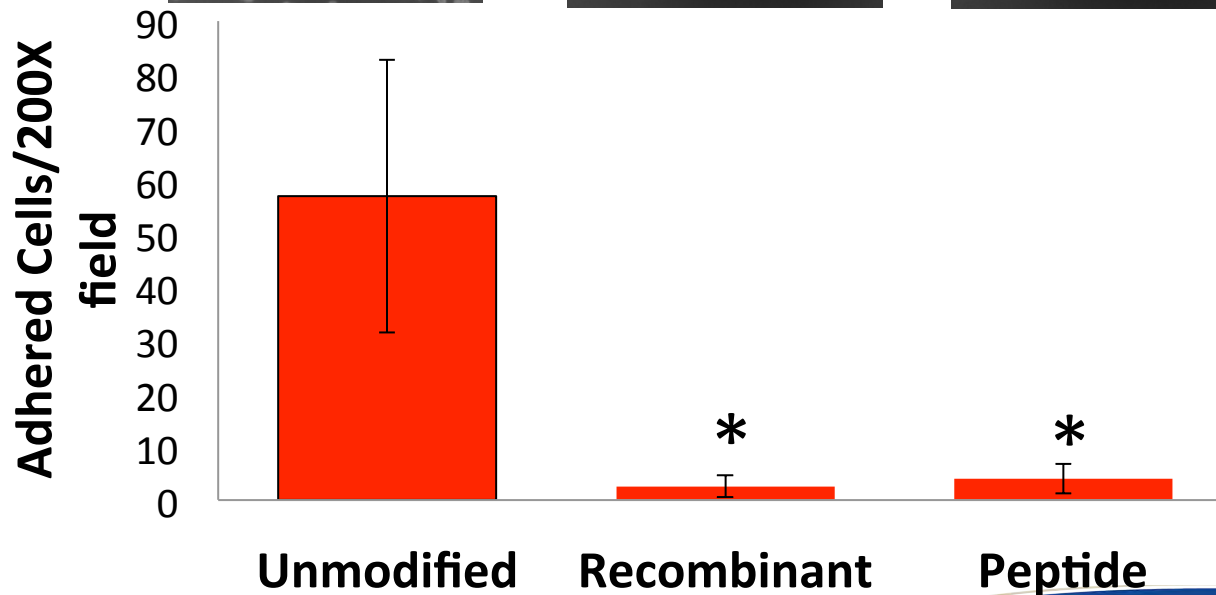
Modified vs  
Control Surfaces

# THP-1 Attachment Assay

A.

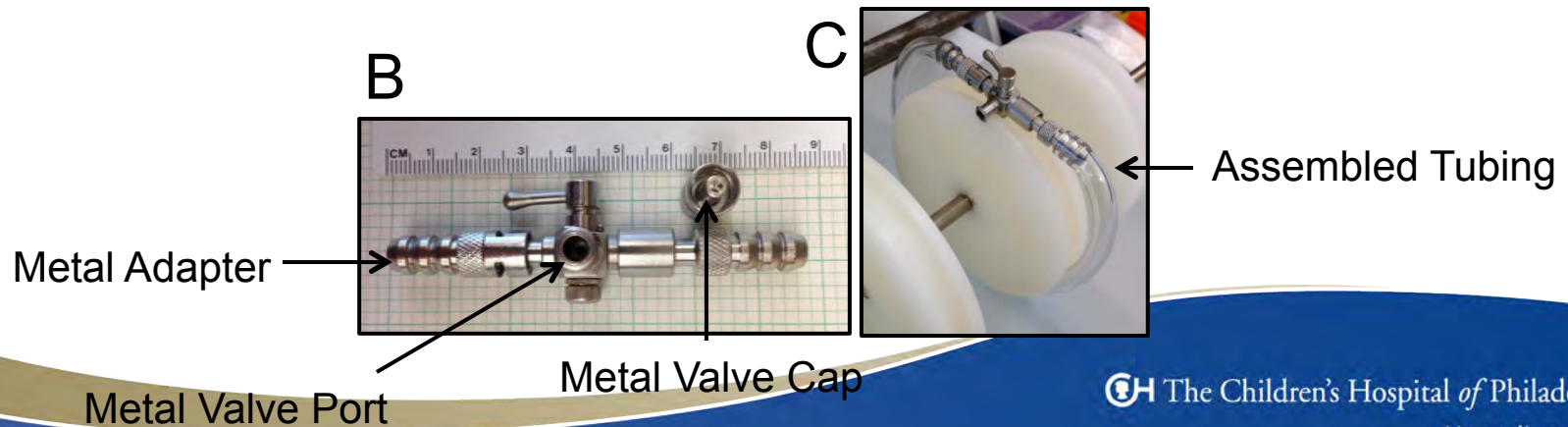
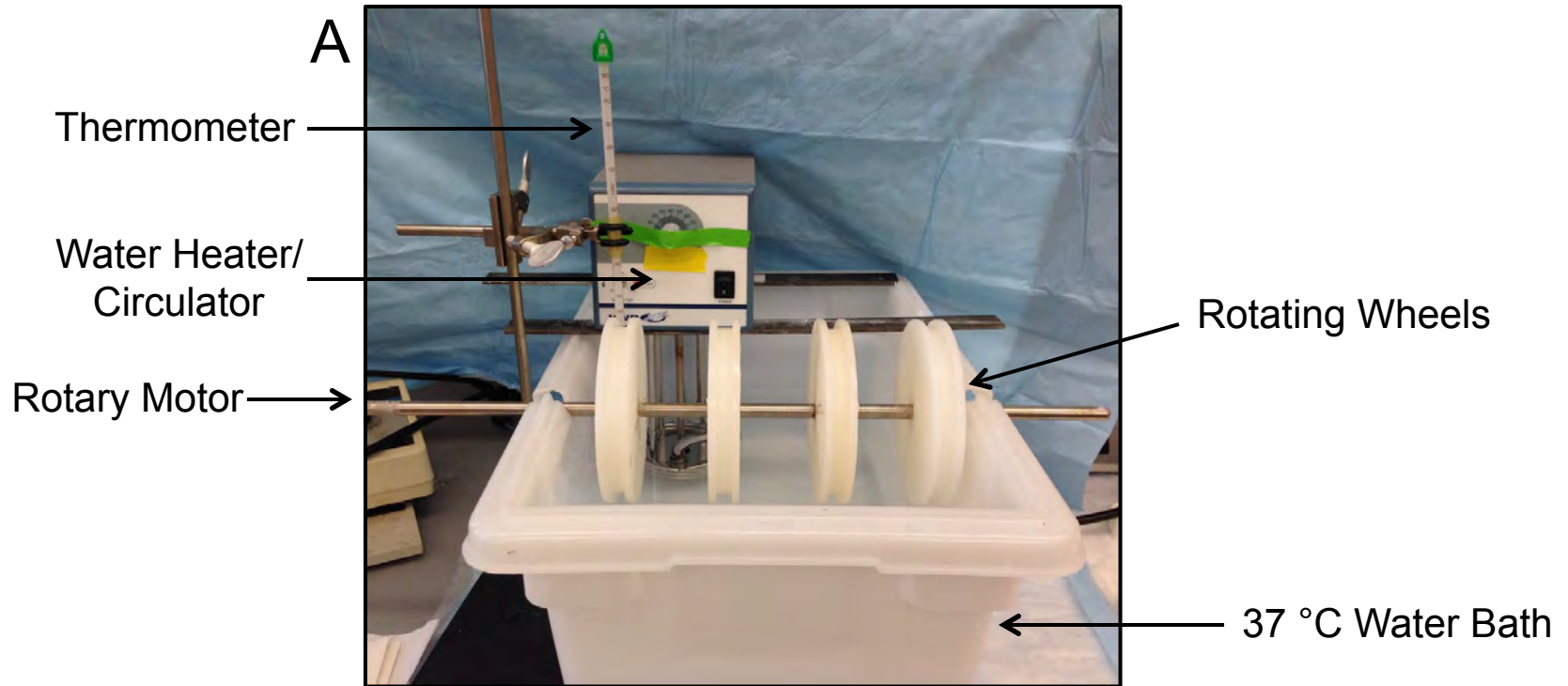


B.



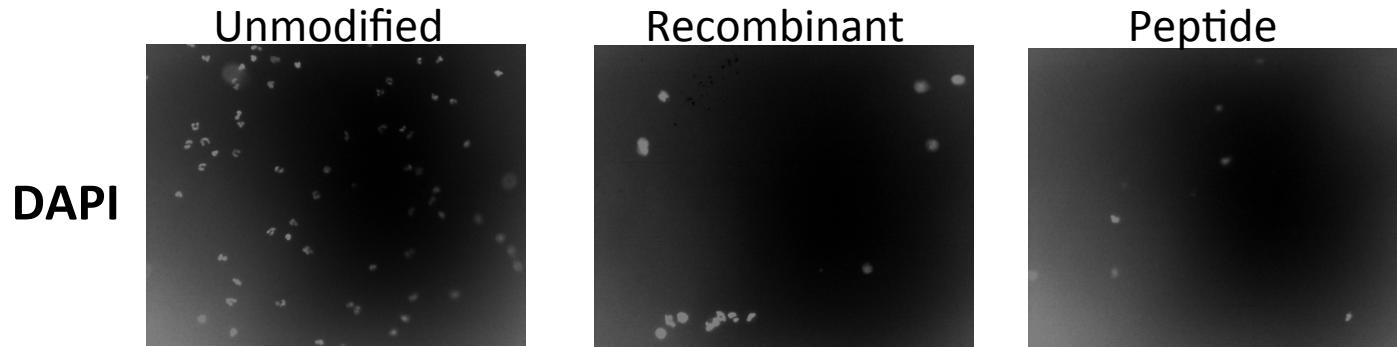
Does CD47 prevent *ex vivo* cell attachment?

# Chandler Loop Experiment

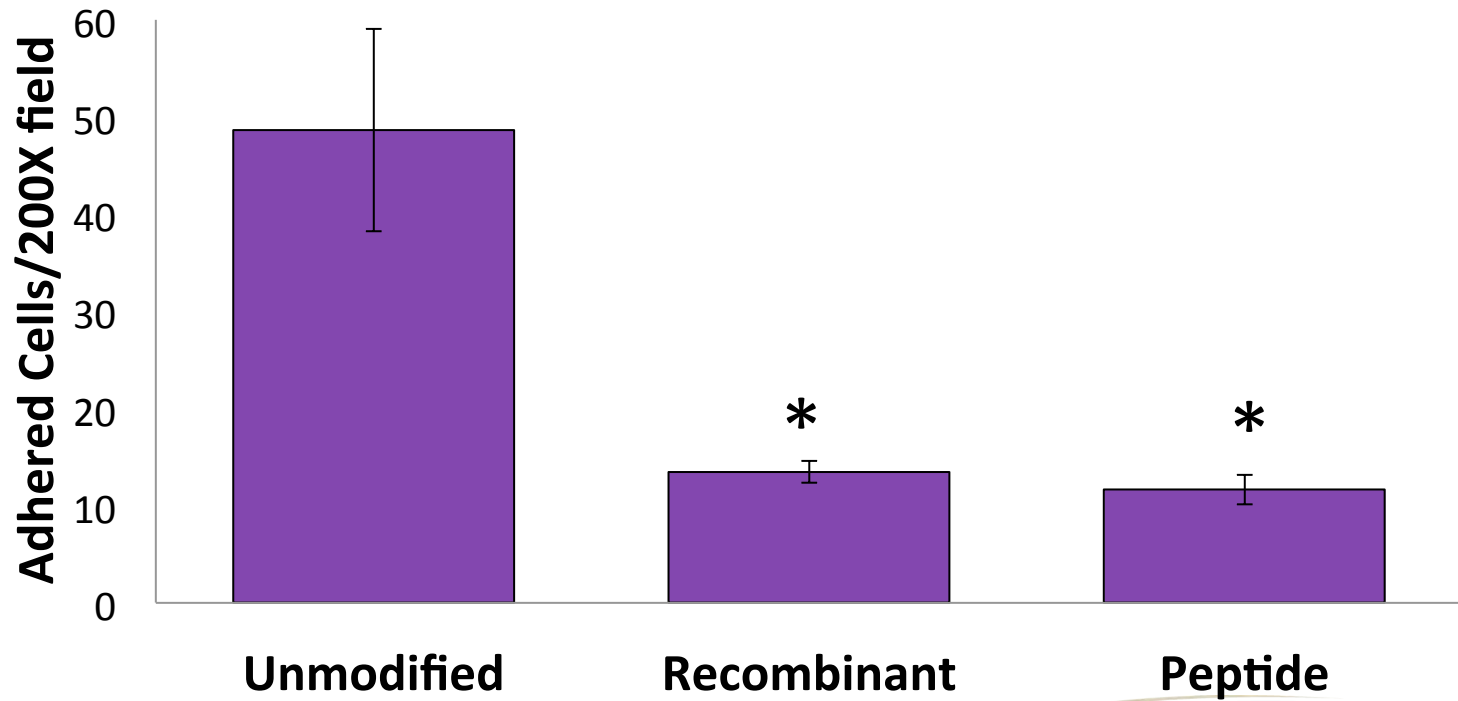


# Chandler Loop Assay

A.



B.



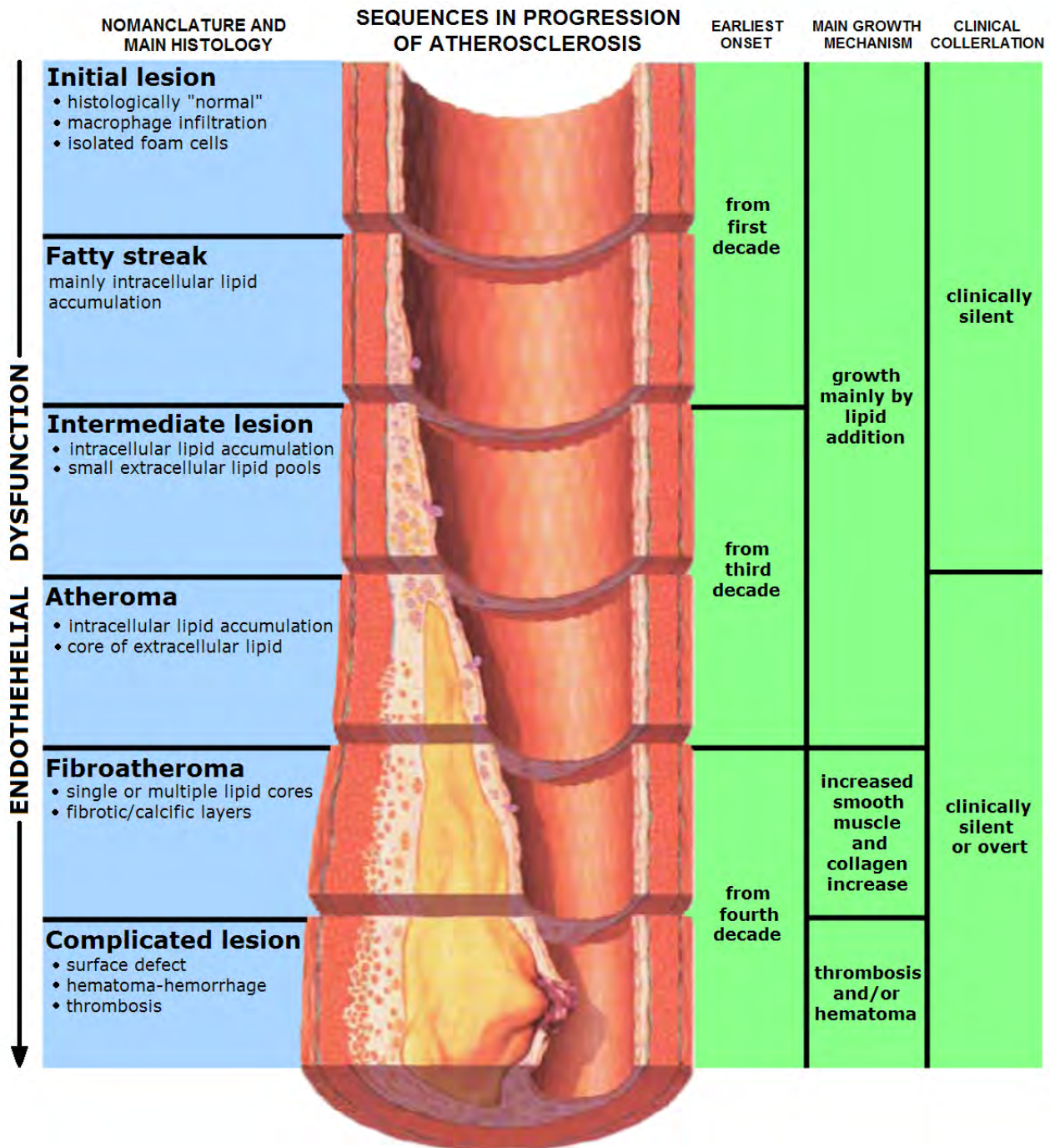


# Summary & Potential Applications

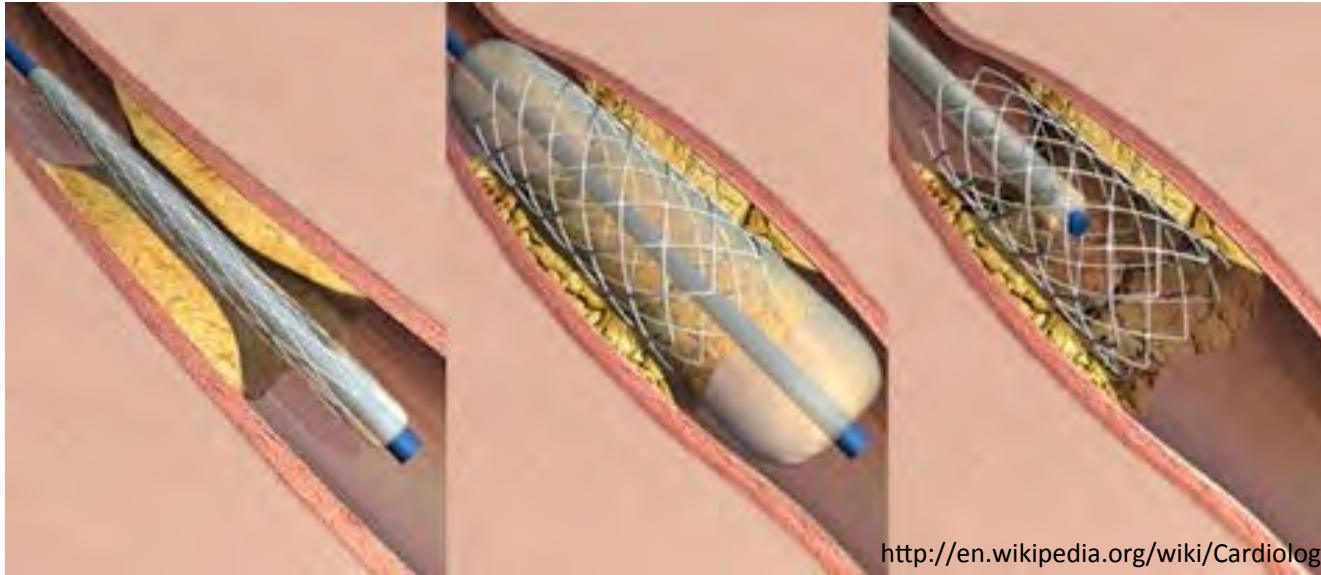
- CD47 prevents inflammatory cell attachment to medically-relevant polymers
- CD47 peptide is a cost effective solution to modifying large surfaces such as cardiopulmonary bypass, hemodialysis, and LVAD tubing.

# The use of CD47 as an anti-inflammatory agent on medical steel

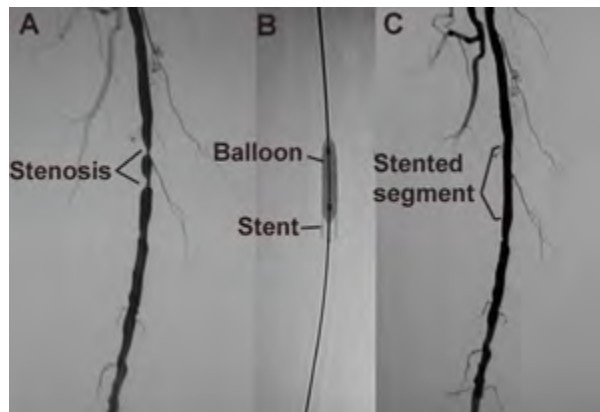
Vascular stents, orthopedic implants,  
dental implants



# Vascular Stents



<http://en.wikipedia.org/wiki/Cardiology>



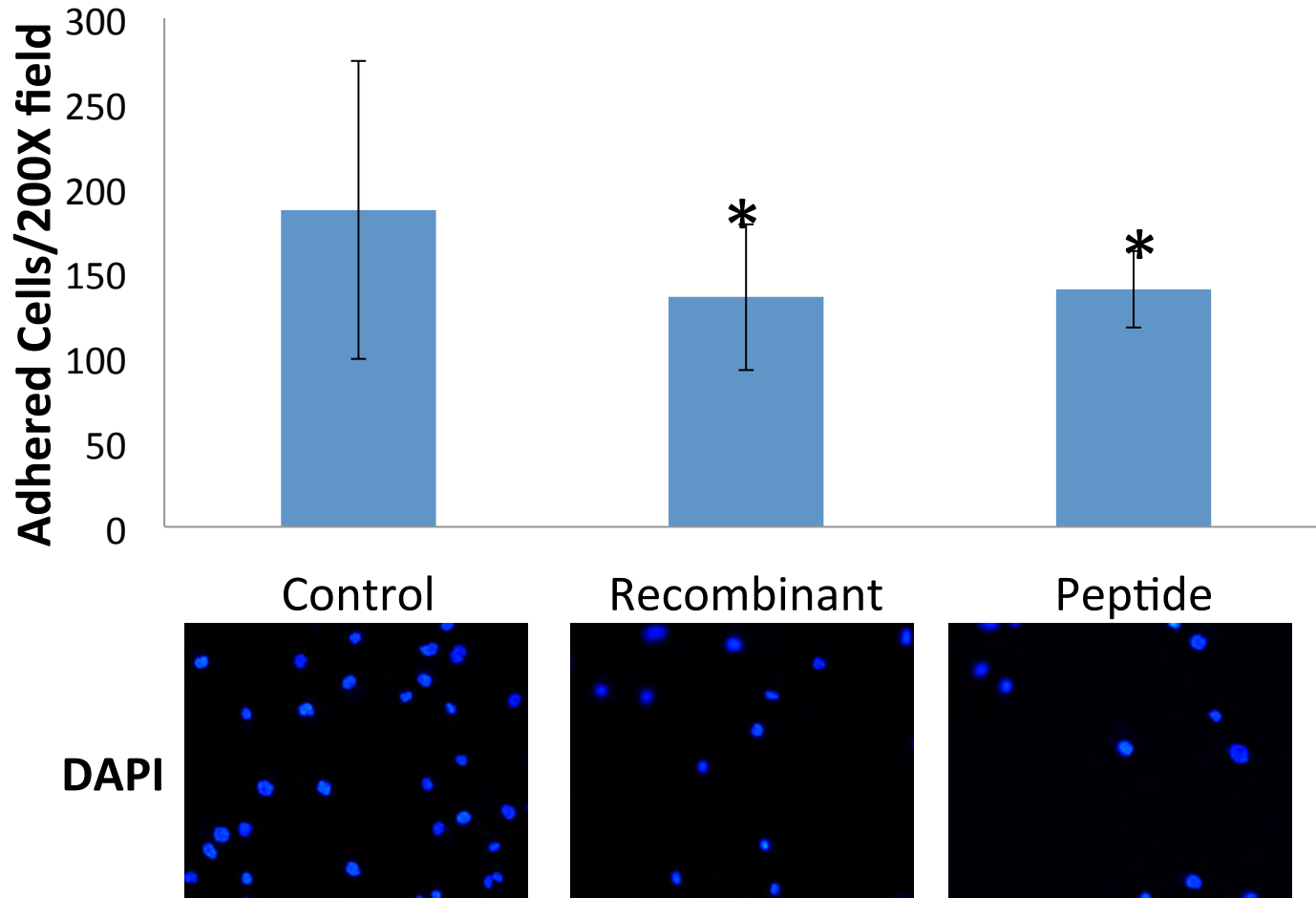
<http://www.yoursurgery.com/ProcedureDetails.cfm?BR=5&Proc=33>



Restenosis

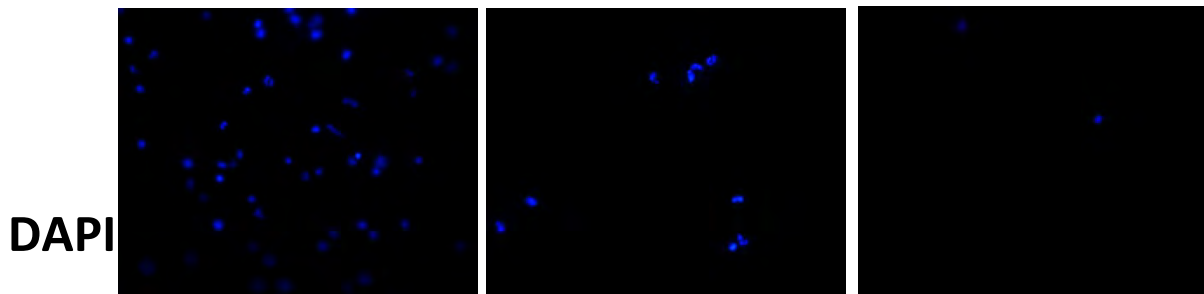
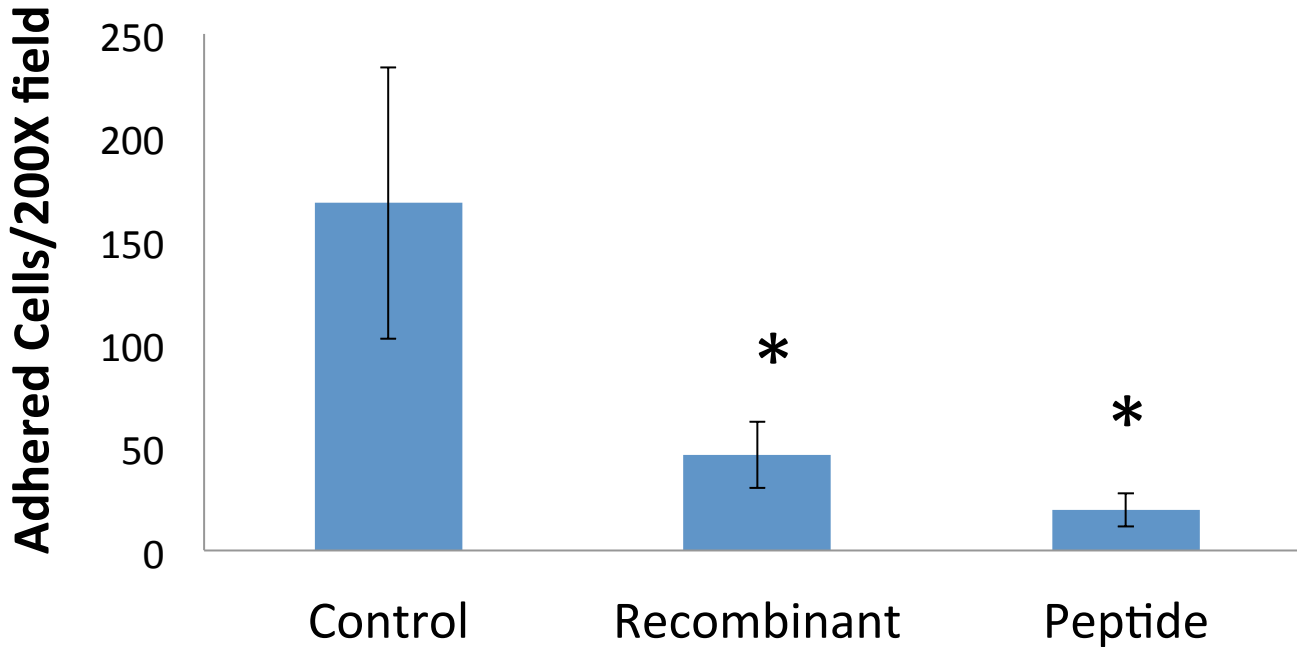
Does CD47 prevent *in vitro* cell attachment?

# THP-1 *In Vitro* Adhesion Assay



Does CD47 prevent *ex vivo* cell attachment?

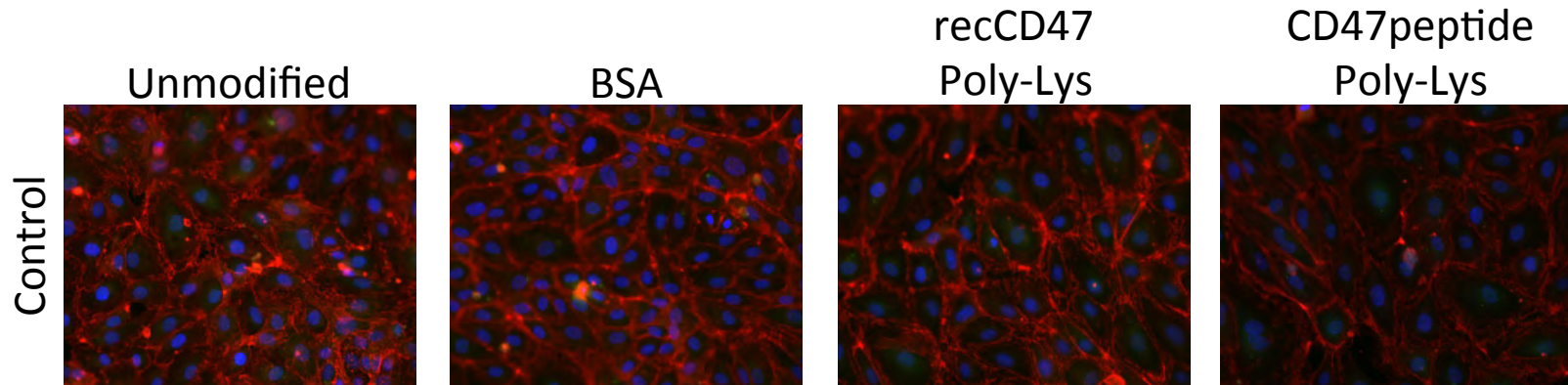
# Human Blood *Ex Vivo* Assay





Does CD47 hinder endothelial  
cell attachment?

# Endothelial Cells on Steel



# Summary and Potential Applications

- Appending CD47 to stainless steel prevents inflammatory cell attachment
- Healthy endothelium forms on CD47-modified steel
- Could be used to prevent restenosis in stented arteries
- Currently being tested *in vivo* in rat model

# Think-Pair-Share

- My research group seeks to prevent inflammatory cell attachment using CD47.
- Individually:
  - Can you think of any other strategies that could inhibit inflammation associated with implanted materials?
    - Hint: Think of the inflammatory response and what is recruited to the site of infection.
- With a partner:
  - Would this strategy work/not work?
  - Problems associated with this strategy?

# Overall Summary

- Pathogens and foreign objects trigger an inflammatory response in the body.
- Innate Immunity (phagocytosis) is the major way the body deals with eliminating pathogens and foreign objects from the body.
- CD47 is a marker of “self” to immune cells.
- CD47 can be used on medical devices/ implantable materials to prevent the inflammatory response.

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# Thank You! Questions?

