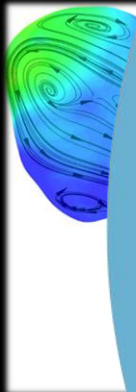
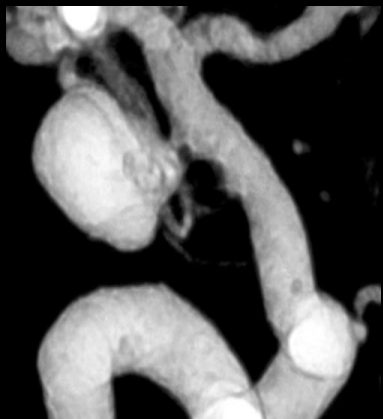


Reconstructed Human Patient Dynamic Models for Engineering Targeted Therapeutics for Aneurysms

Associate Prof. Netanel Korin

Cardiovascular Nano-Med
Engineering Lab

BRAIN ANEURYSM

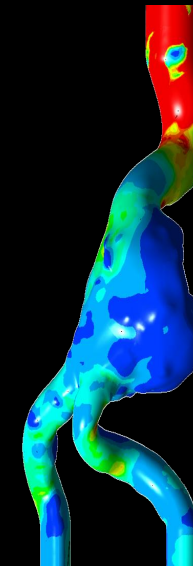


Cardiovascular
Disease



In-Vitro
Modeling and
Pathological
Flow Study

AORTIC ANEURYSM



Leveraged Approach for
Localized Treatment

STROKE

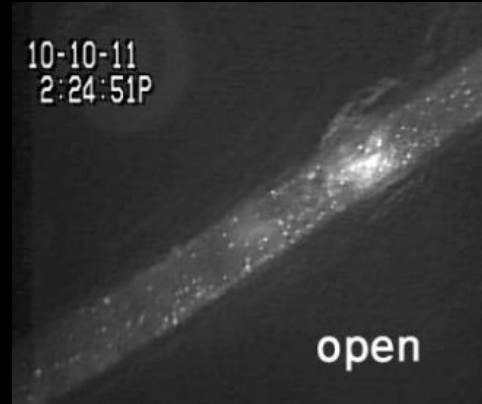
AORTIC ANEURYSM



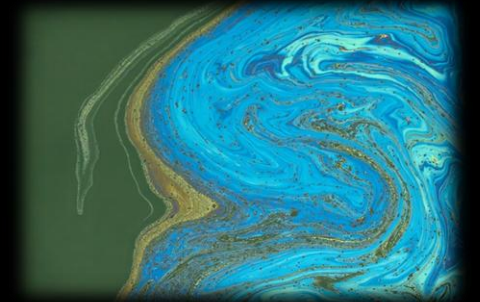
**Deposition in
Circulation zones**



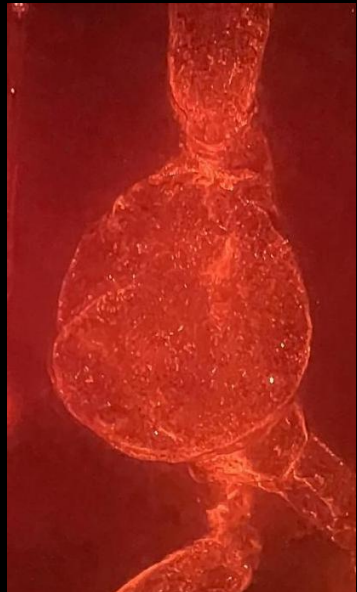
**Shear activated
therapeutics**



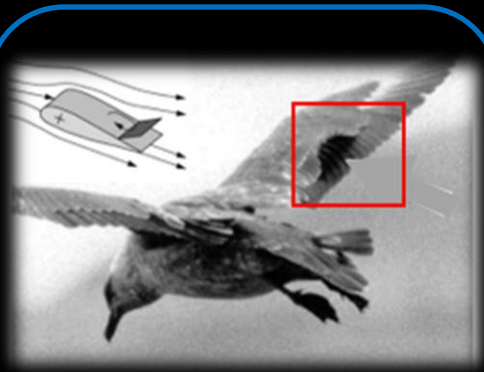
BRAIN ANEURYSM



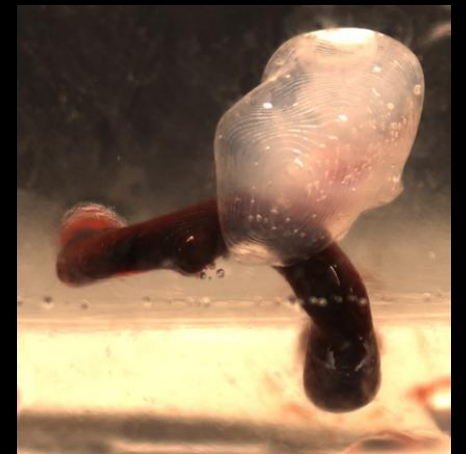
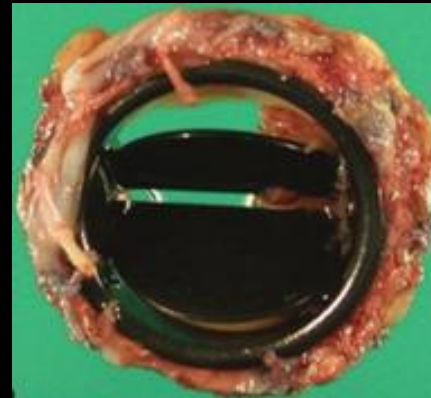
Surface Tension Isolation



PROSTHETIC VALVE THROMBOSIS



Flow Control



SHEAR INDUCED DRUG DELIVERY (ARTERIAL STENOSIS)

Platelet activation

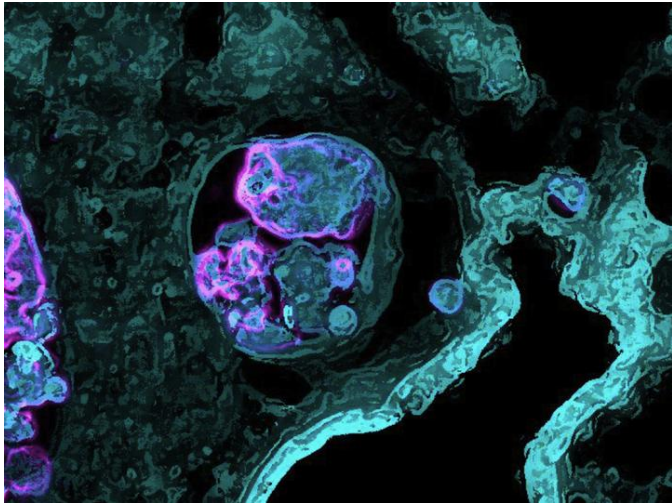


Shear



The Bio-physics of Vascular Disease: Localized Treatments and Technologies

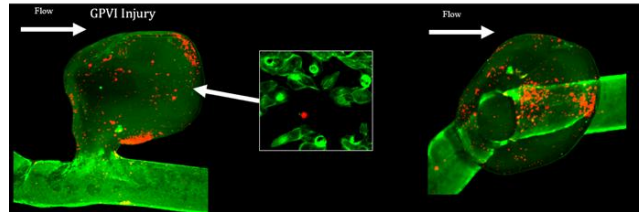
Targeted Drug Delivery/ Nanomedicine



Technology/ Engineering

Korin et al. ,JAMA Neurology, 2015
Khoury et al. ,JCR, 2020

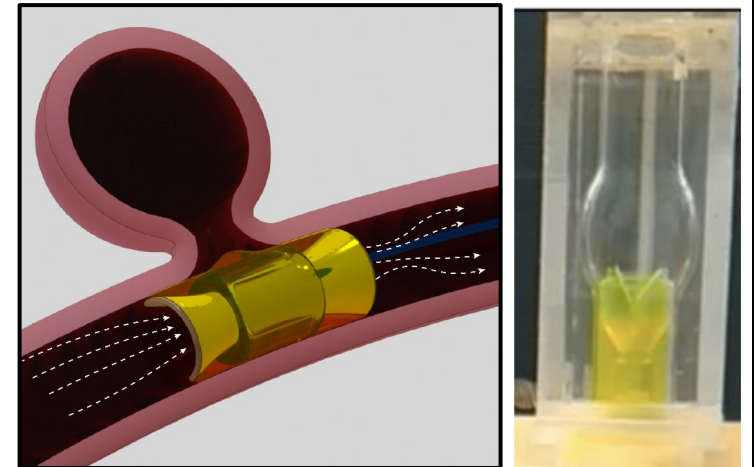
Human Disease Models: In vitro Dynamic Models



Basic Understanding

Korin et al., Science, 2012
Epshtein et al., BioTM, 2021

Intraarterial Treatment of Large Vessels/**Devices**



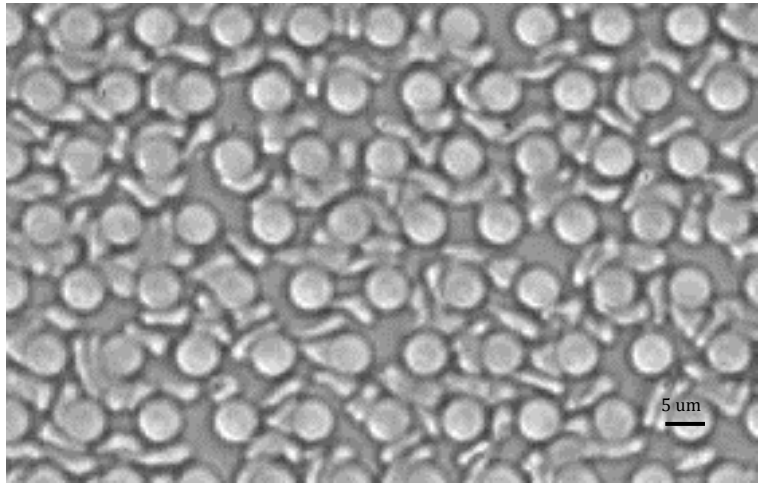
Technology/Engineering

Patent US20210236140A1, 2021
Patent US 20230255753A1 , 2023

Biophysics and Blood flow in Cardiovascular Disease-> Targeted Therapeutics (+ Devices)

Dynamic In Vitro Human Physiological Models of Disease

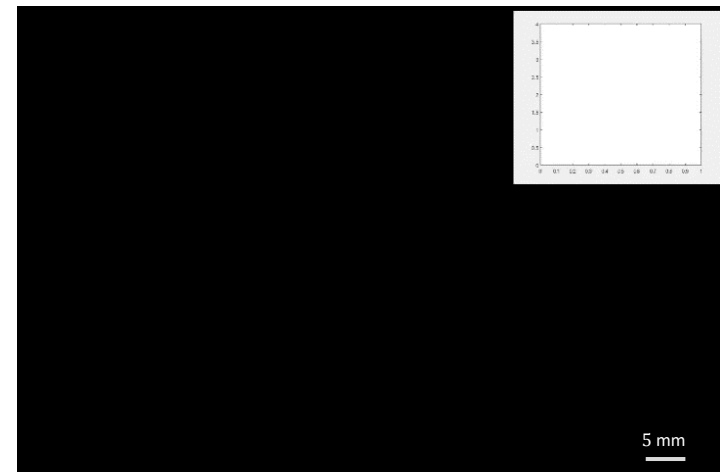
Lung Capillary Networks
RBC carriers + Deformable carriers



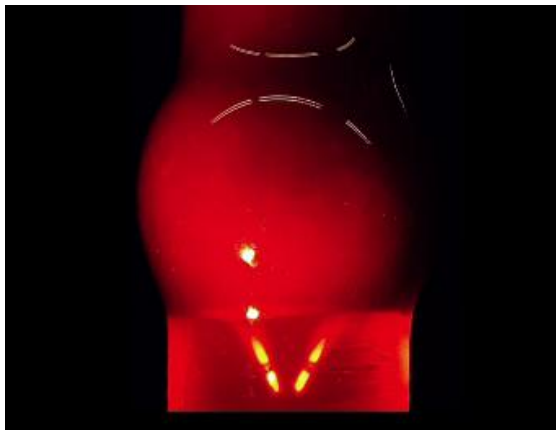
Injury Sites/Thrombosis
Biomechanical inhibition and Drug Delivery



Arterial bifurcations (Atherosclerosis)
(Targeted Delivery + Stent design and therapeutics)



Heart Valves
Self cleaning Valves/devices



Brain and Abdominal Aneurysms
(Target delivery + biophysical isolation)



Cerebral aneurysms

An excessive localized enlargement of an artery caused by a weakening of the artery wall.

- The risk of rupture is only 5% (Adasivan et.al 2013).
- The fatality rate of ruptured aneurysms is over 50%

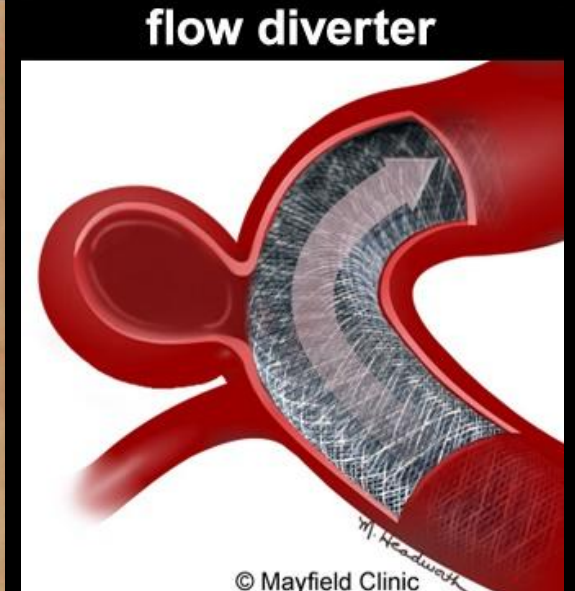
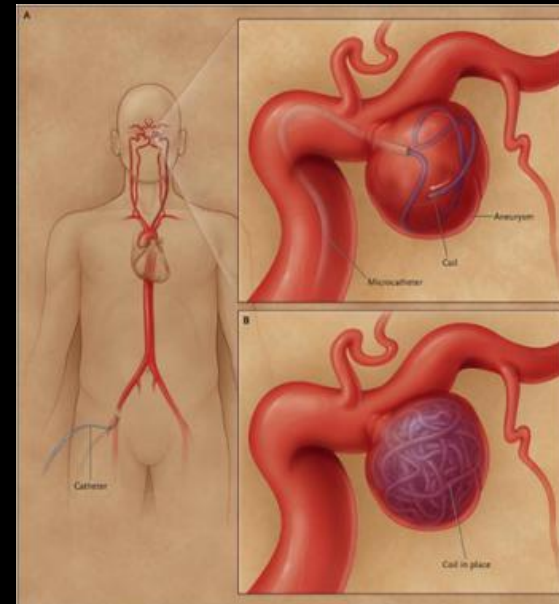
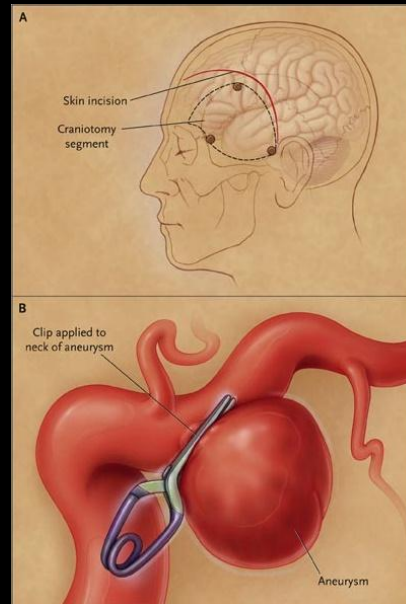


Graham Johnson
medical media

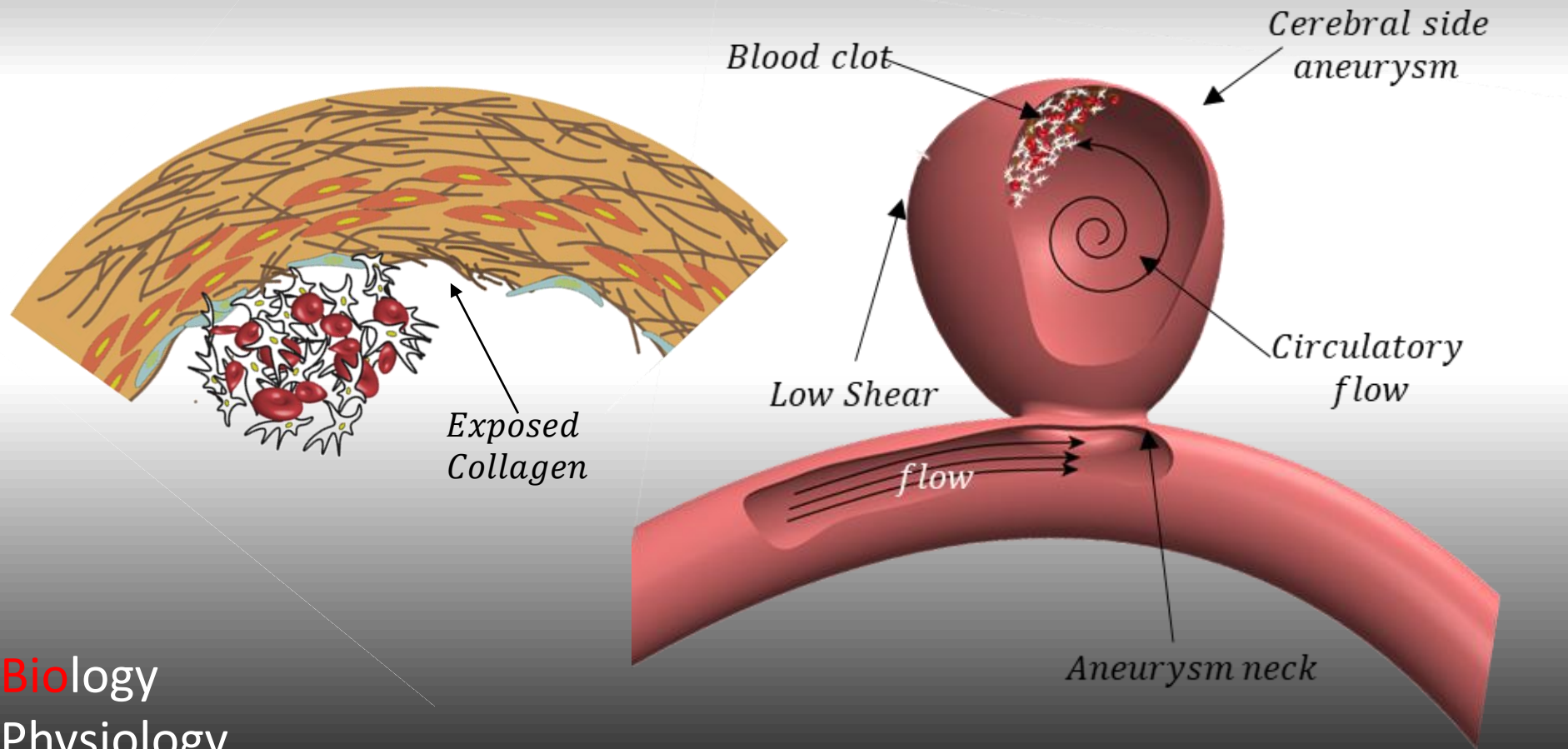
<https://www.grahamj.com/>

Current Available Treatment:

- Clipping
- Coiling
- Stenting and flow diverting



Biophysics of High-Risk Cerebral Aneurysms



**Deposition in
Circulation zones**

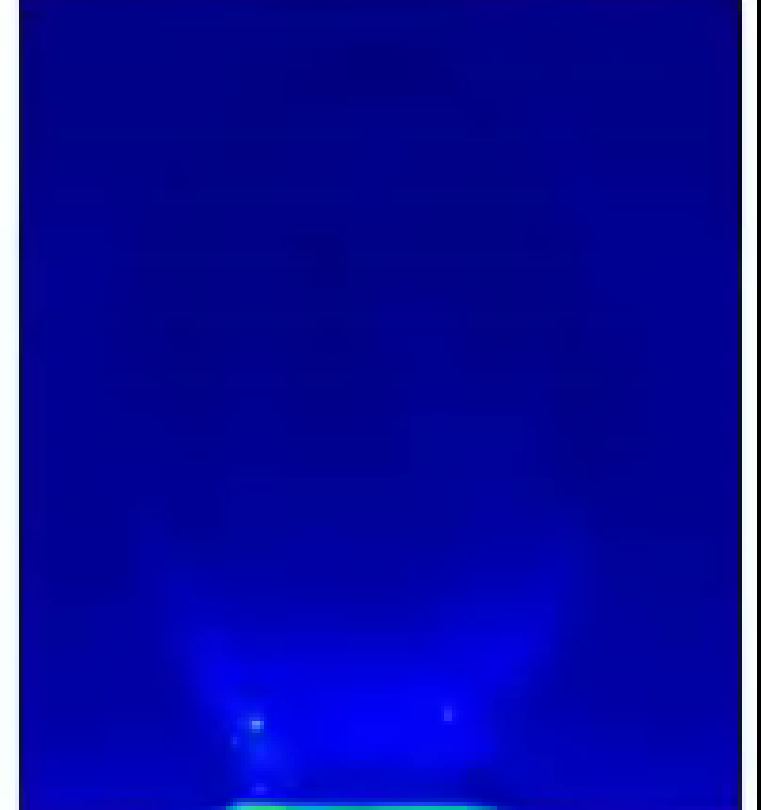
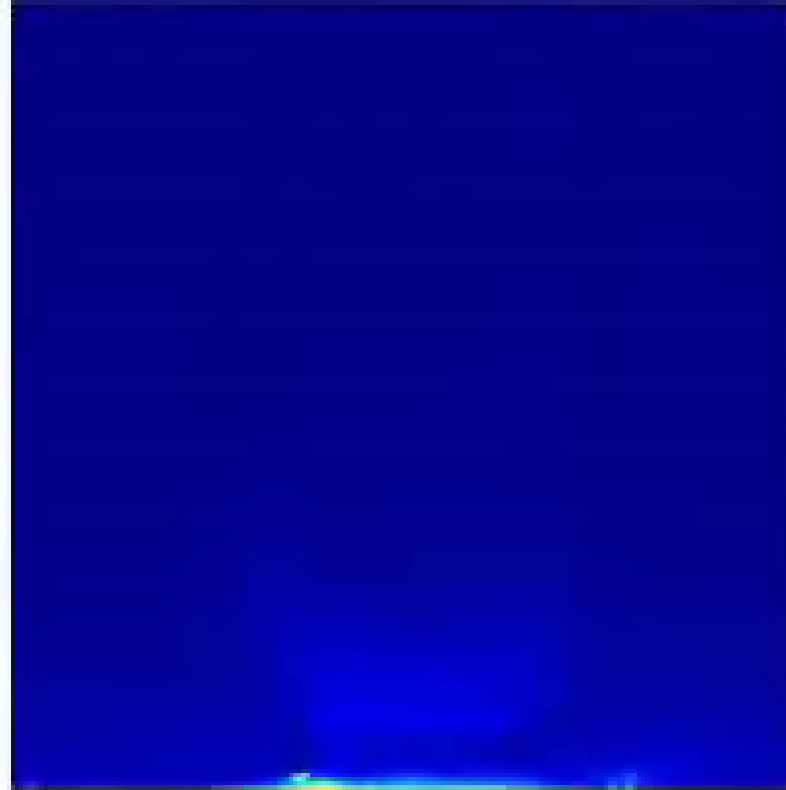
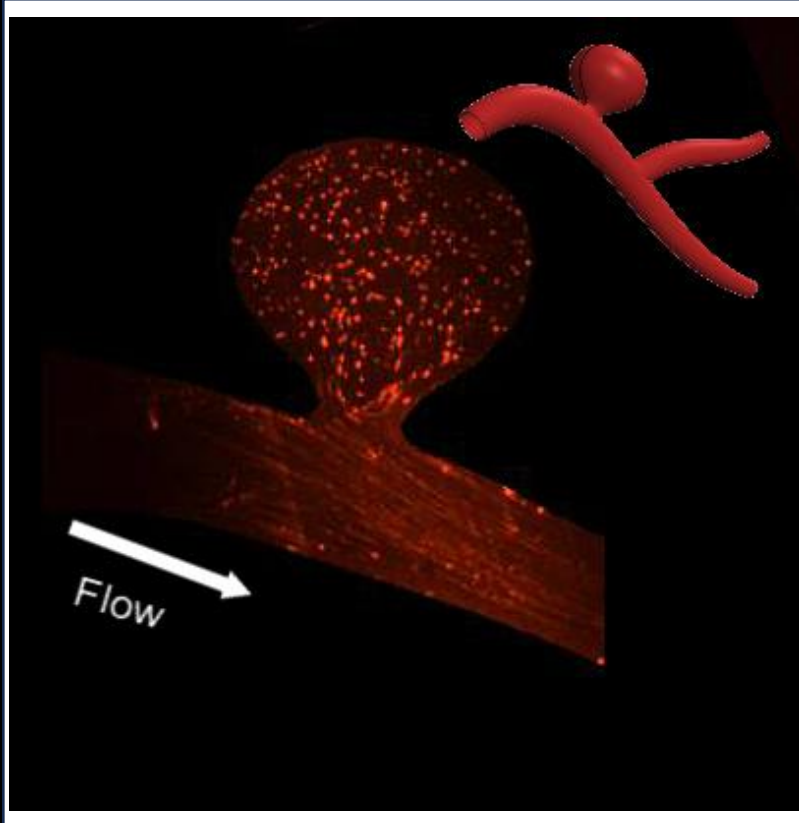
Biology
Physiology

Physics
Mechanics

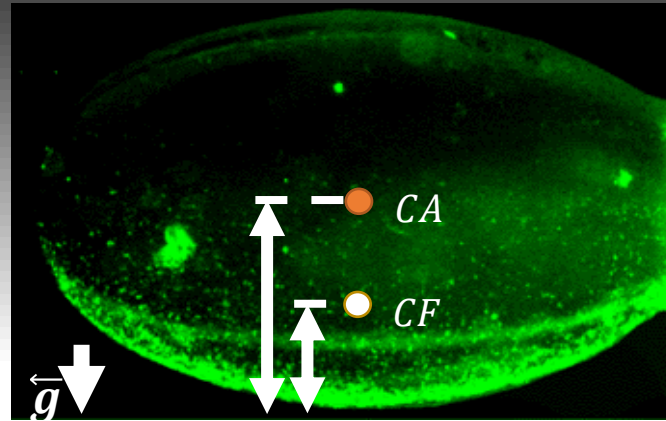
Aneurysm Flow Patterns and Transport Properties

Particles

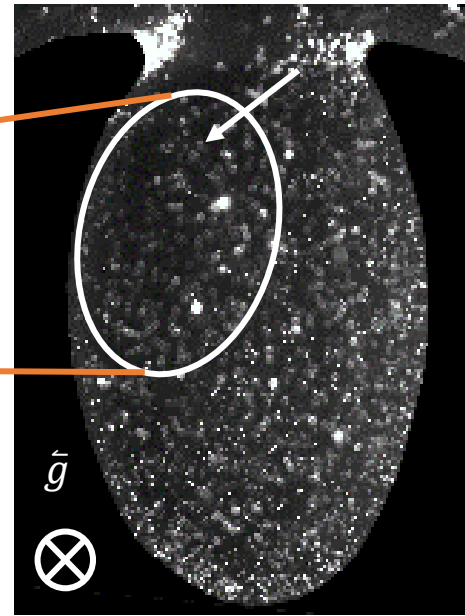
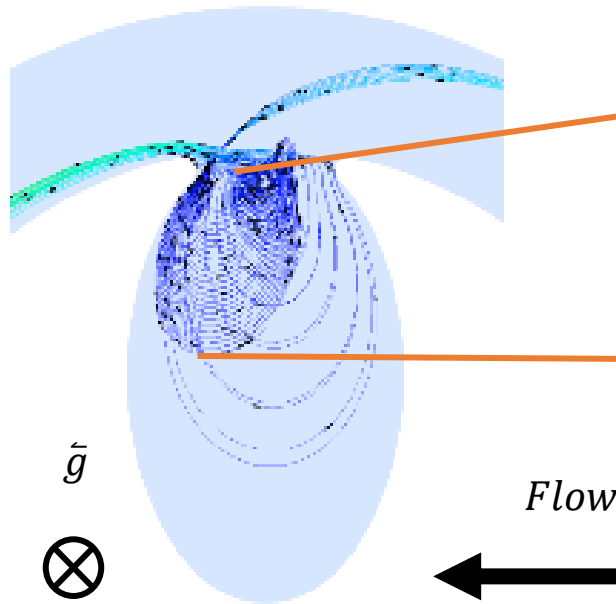
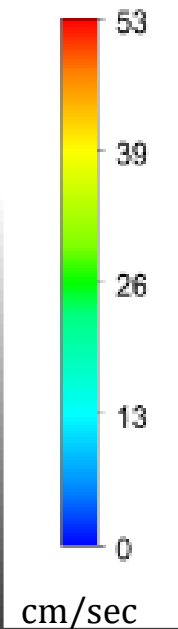
Dye



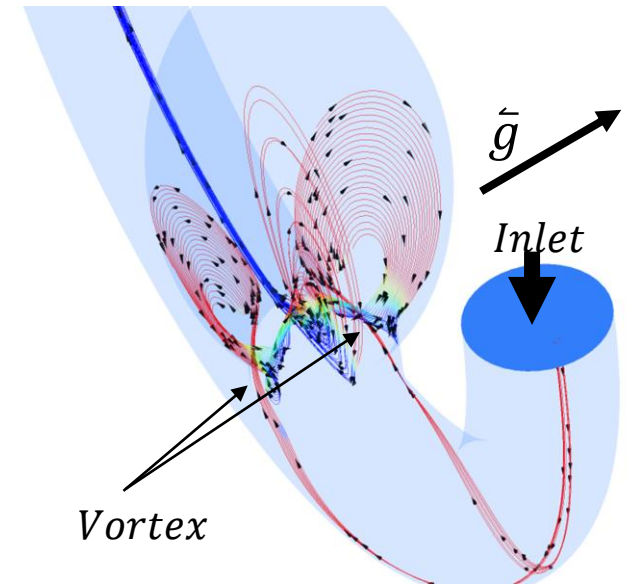
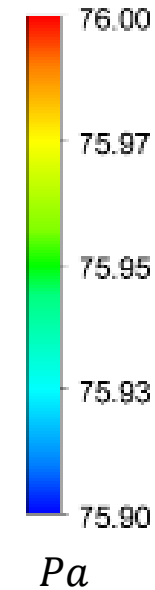
Deposition of Particles/Cells in Aneurysm Cavities



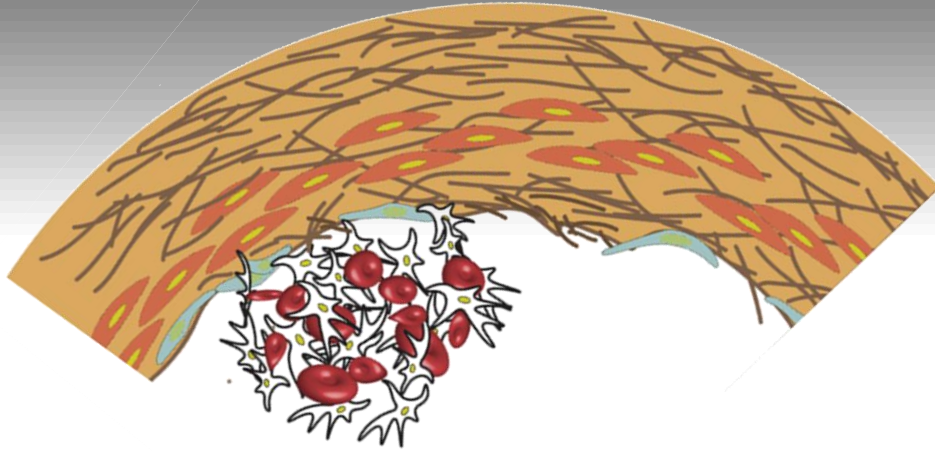
Velocity



Pressure



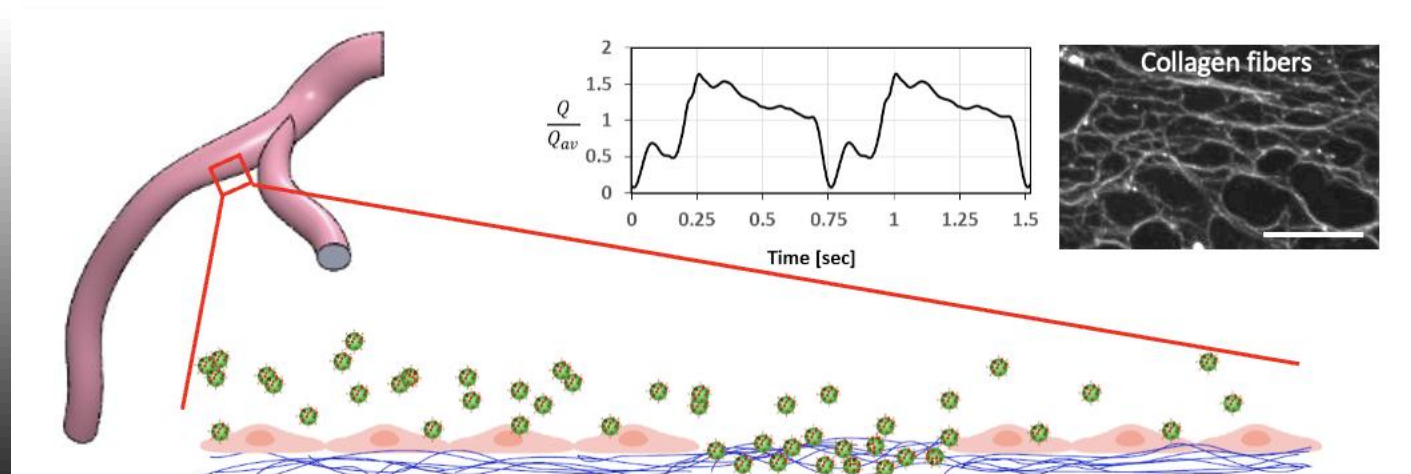
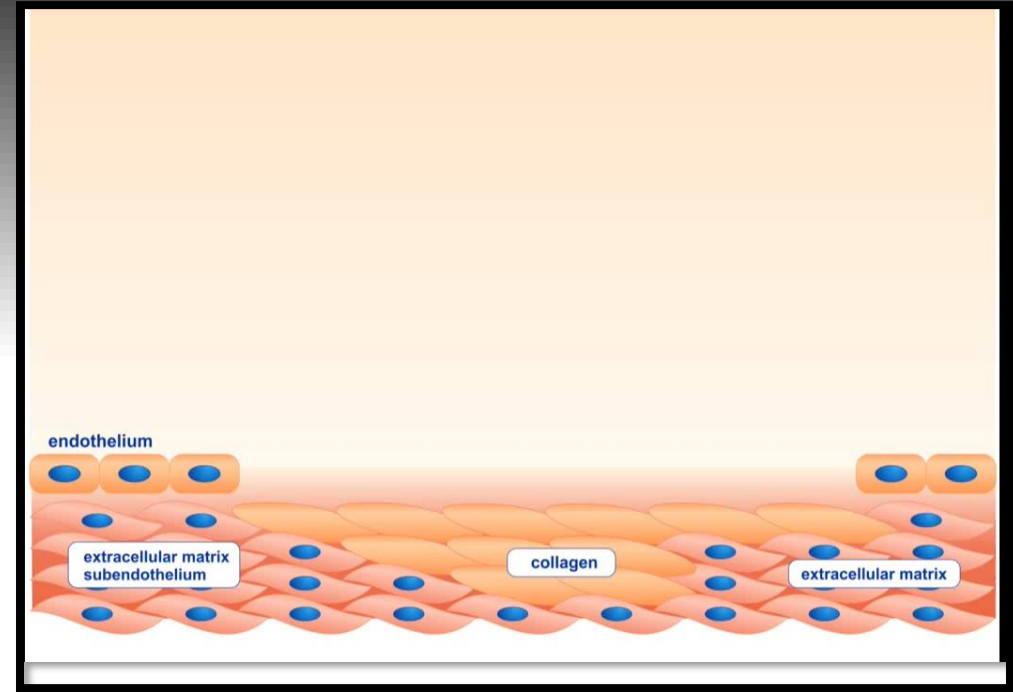
High Risk Aneurysms and GPVI functionalized Particles



Prof. Meinrad Gawaz
University of Tübingen

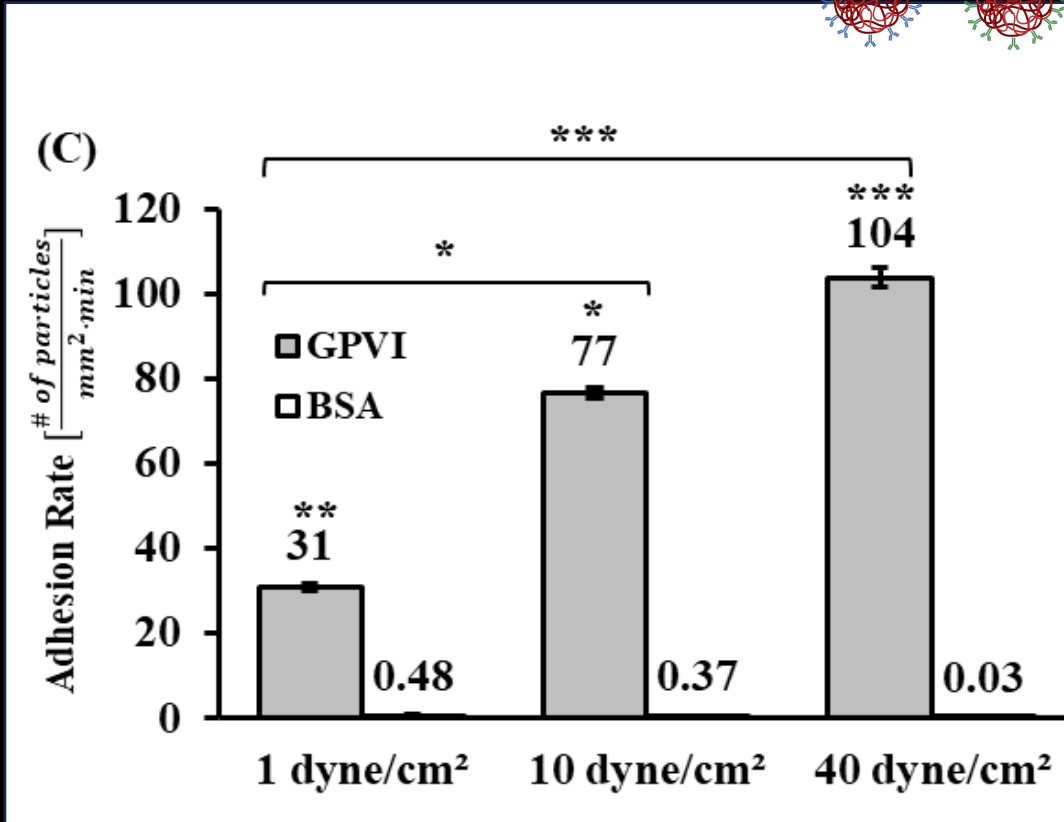


EBERHARD KARLS
UNIVERSITÄT
TÜBINGEN



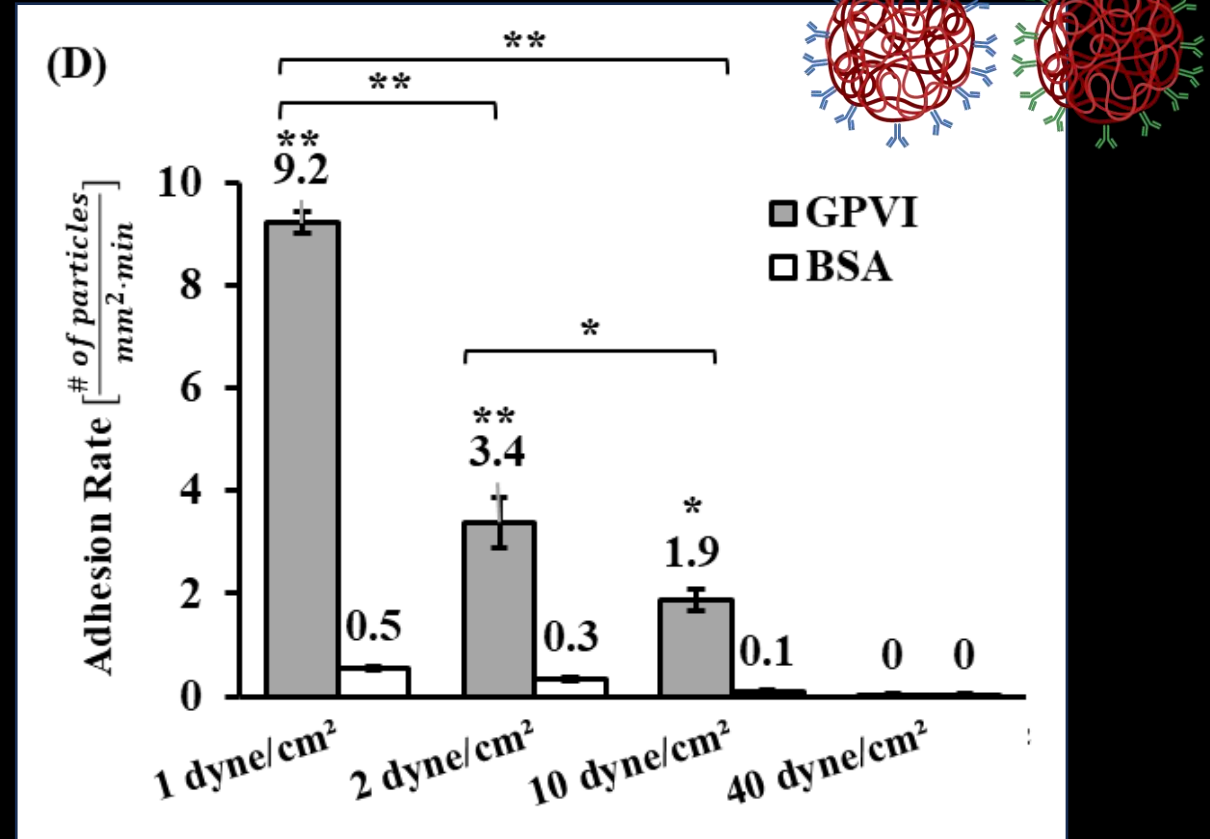
Shear Adhesion of GPVI Carriers

PLGA_v 200 nm Particles GPVI vs. BSA



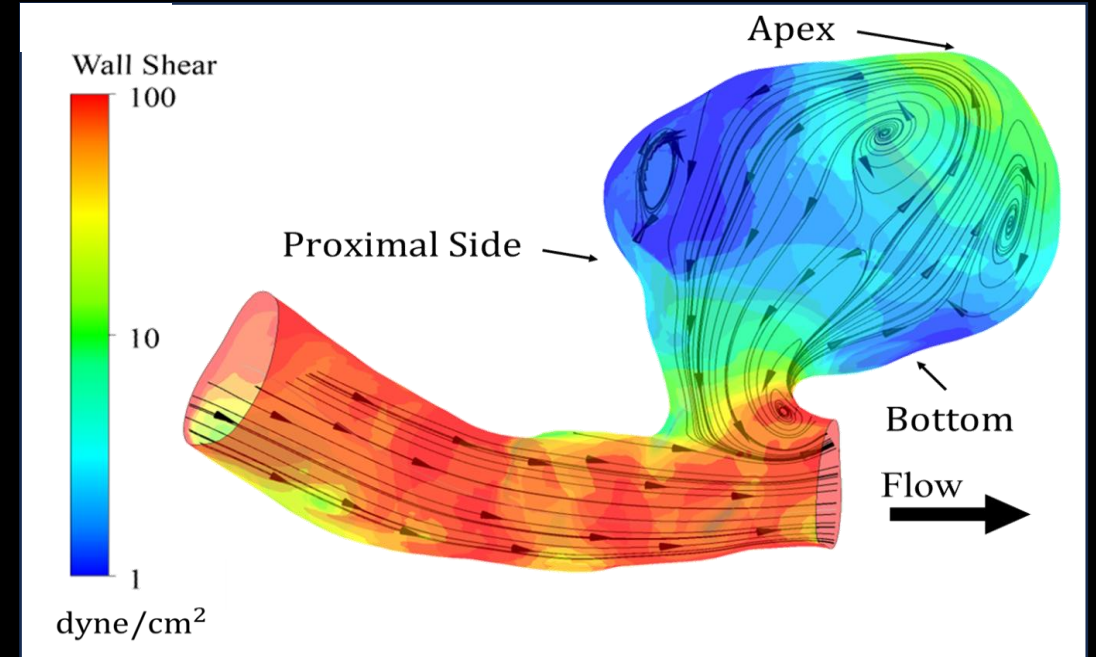
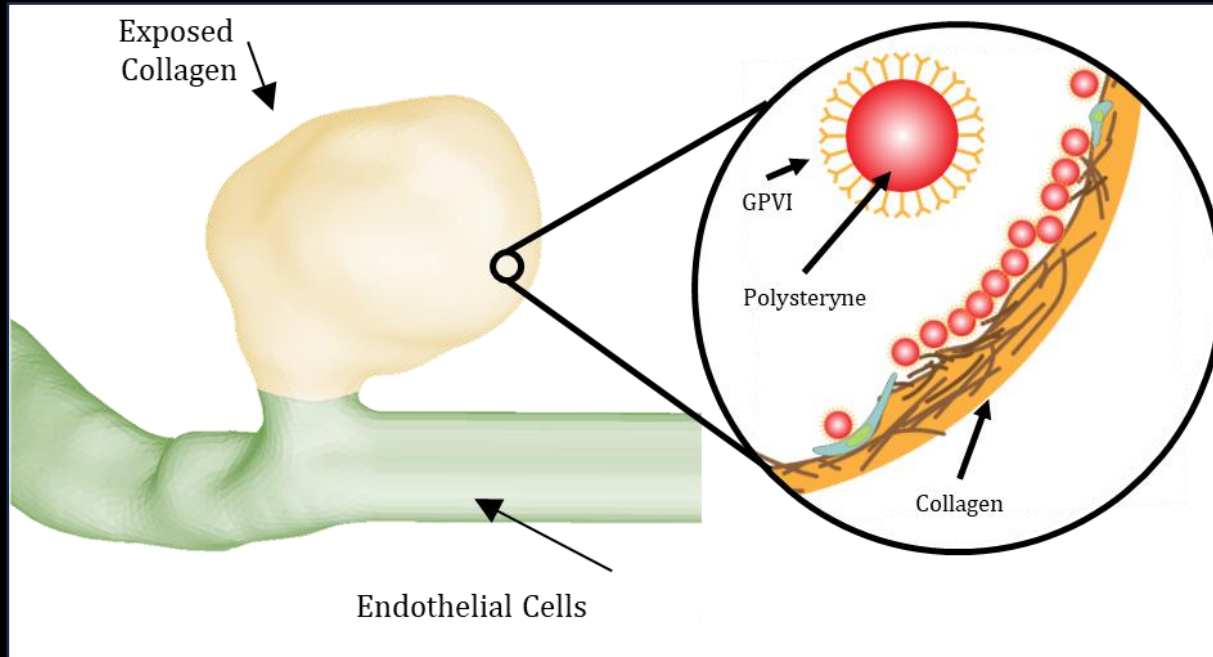
→ High Shear Targeting

2 µm Particles GPVI vs. BSA



→ Low Shear Targeting

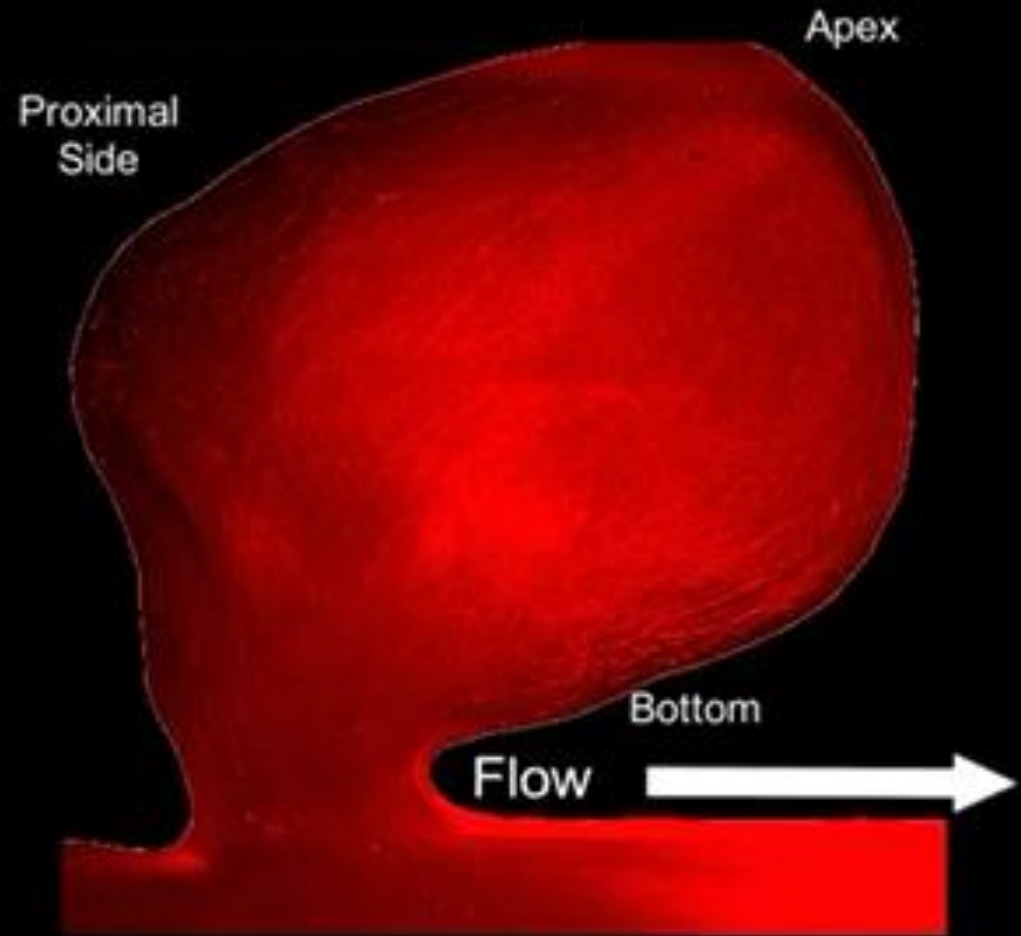
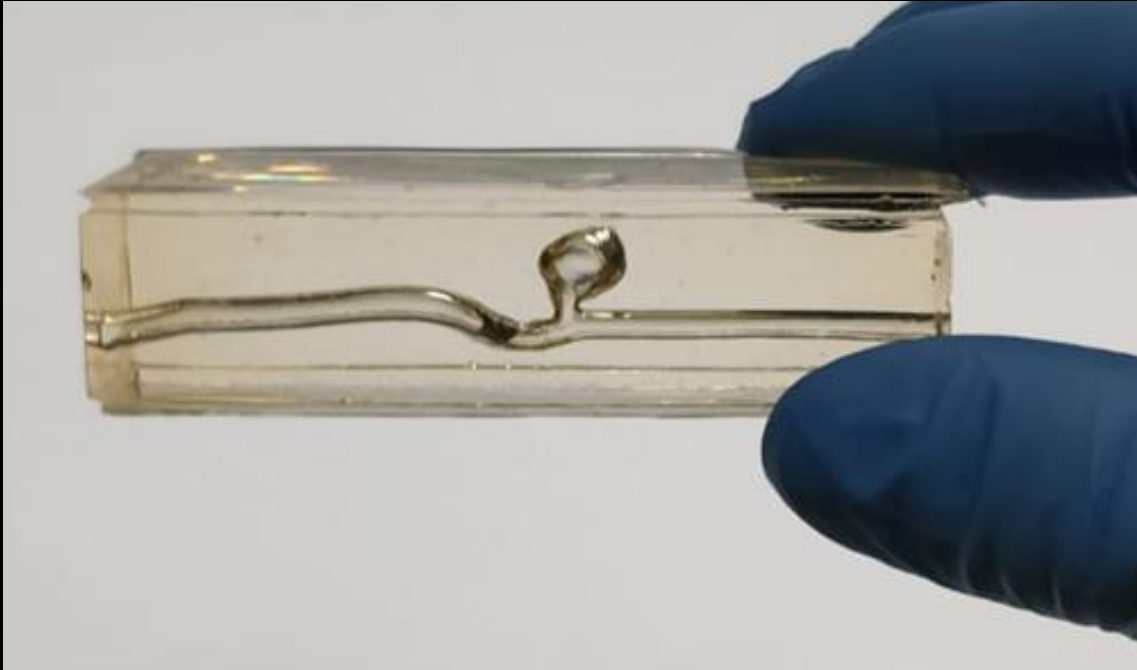
Biophysical GPVI Targeting –In Vitro



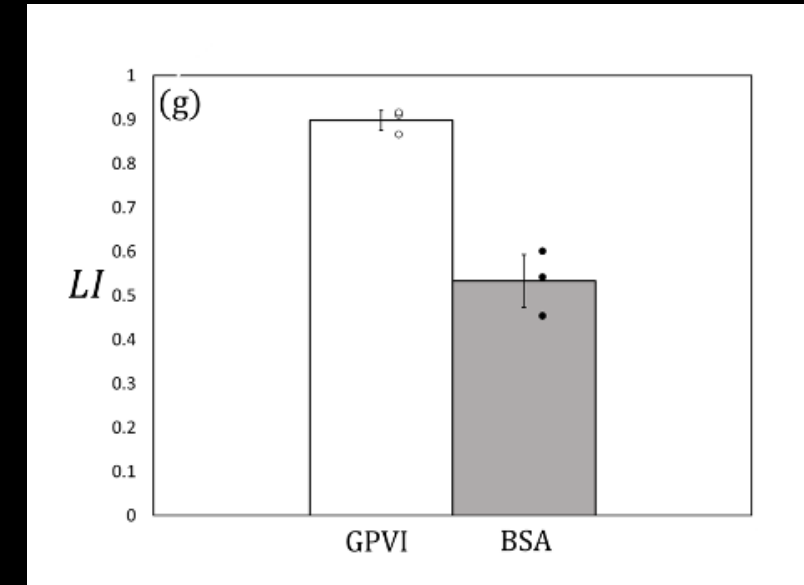
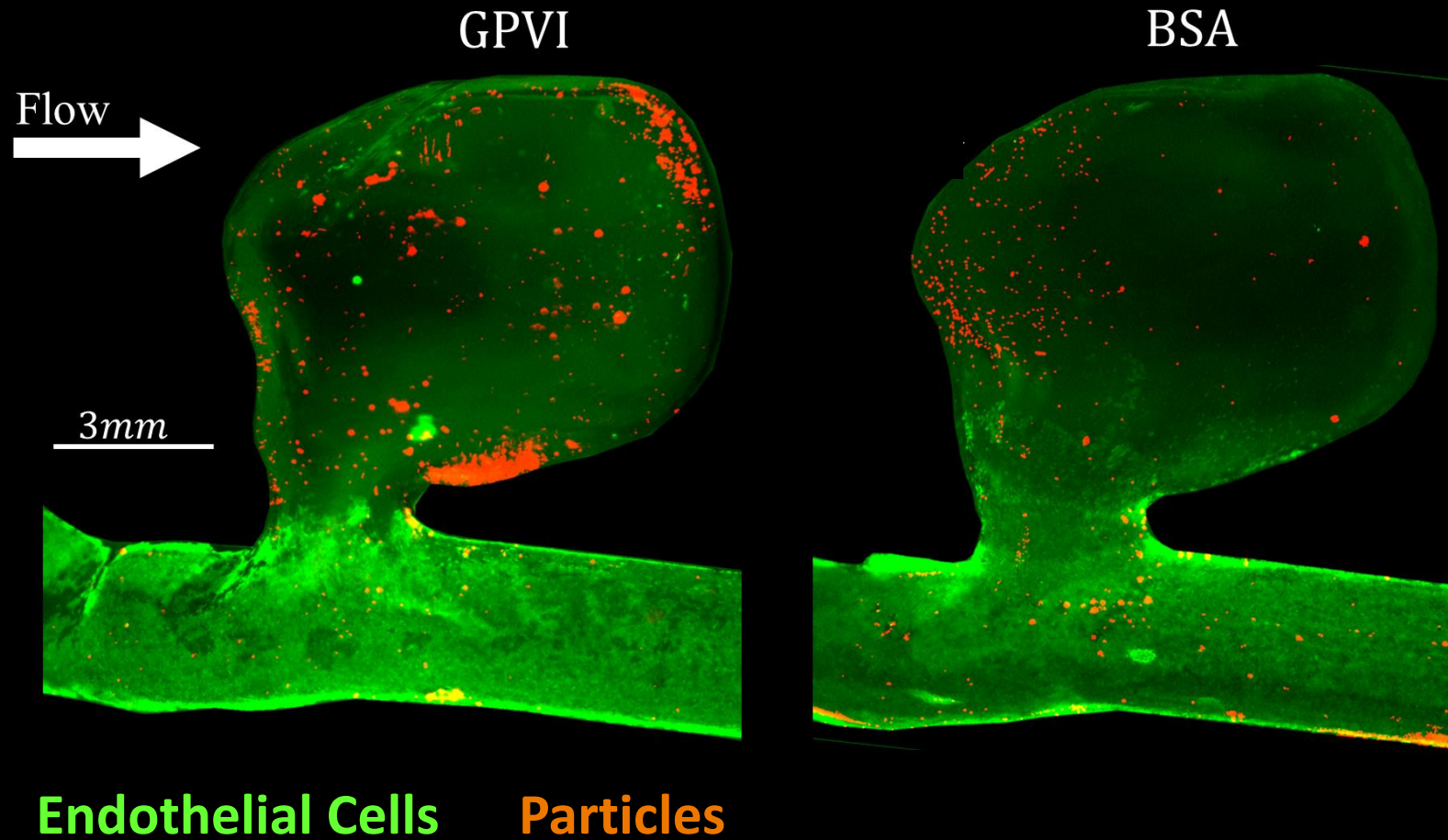
Biology
Physiology

Physics
Mechanics

Biophysical GPVI Targeting –In Vitro



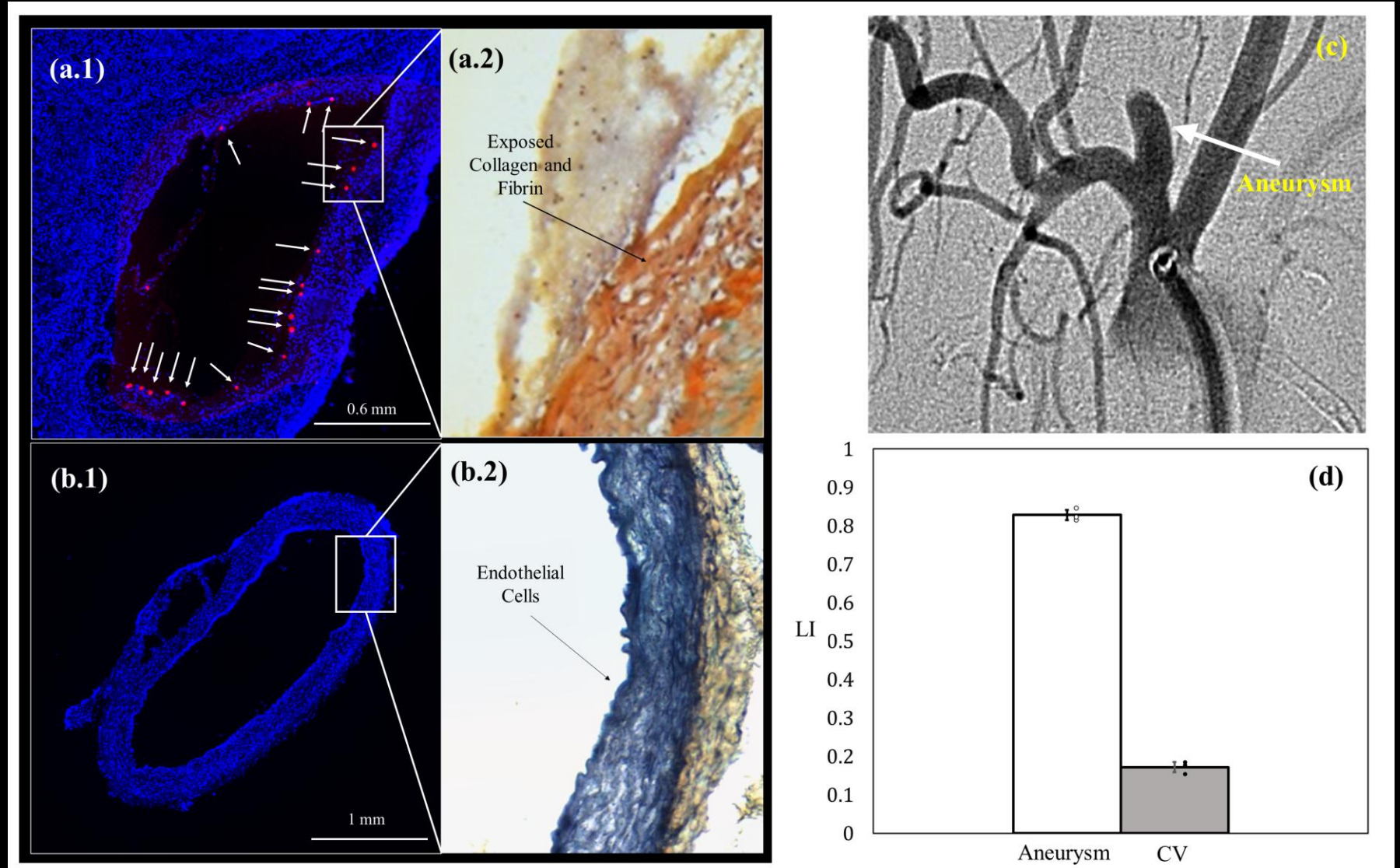
Biophysical GPVI Targeting –In Vitro



In-Vivo



Matthew Gounis, PhD.
Umass Medical School

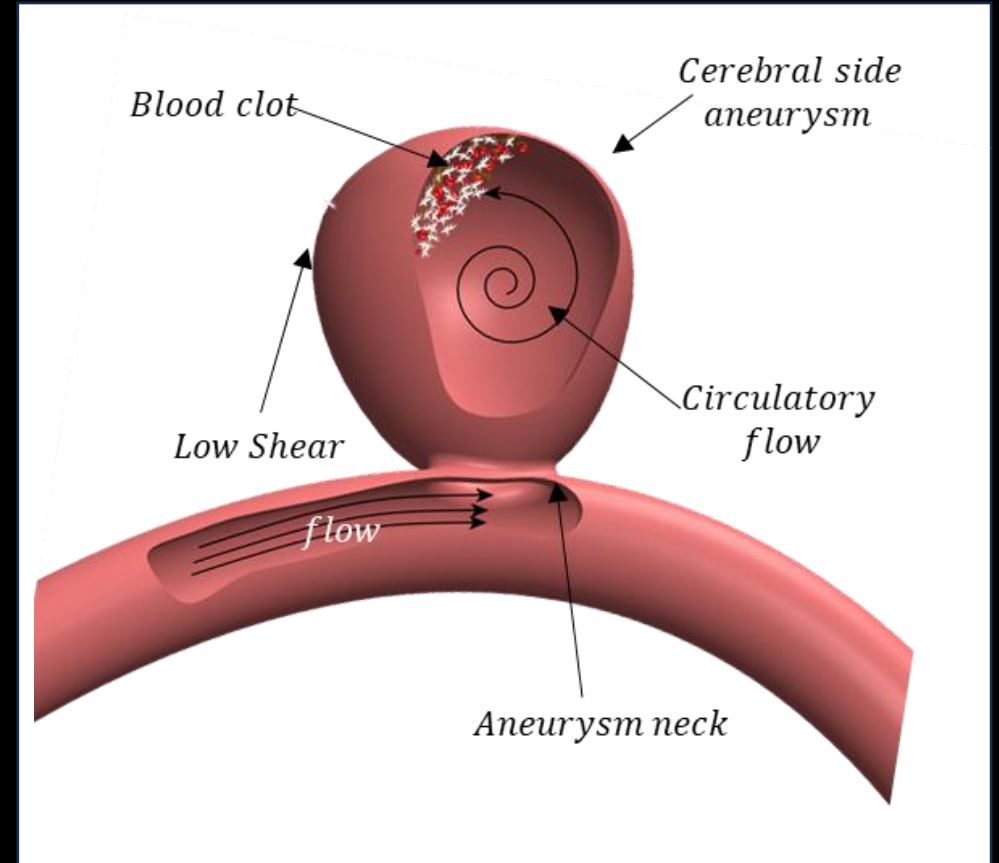


Gap: To Treat or Not to Treat... How to Treat?

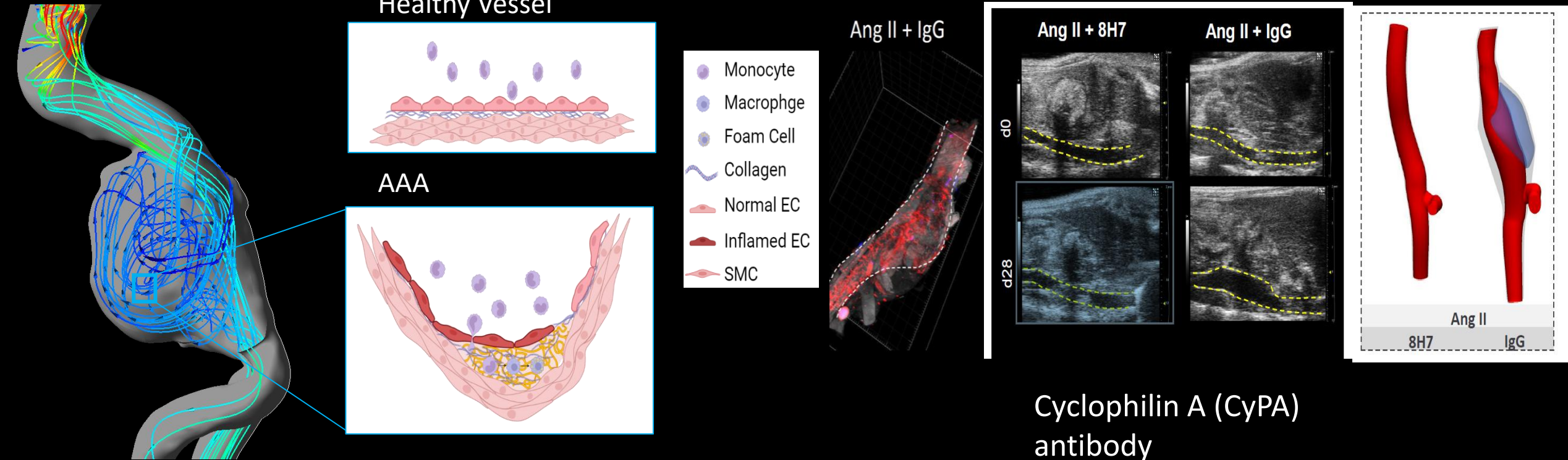
- Need for detection of high-risk Aneurysms
- Need for treatment of Aneurysms that are not considered of high risk

What to Deliver?

Inflammation
Thrombosis
Injured Vessel
Wall

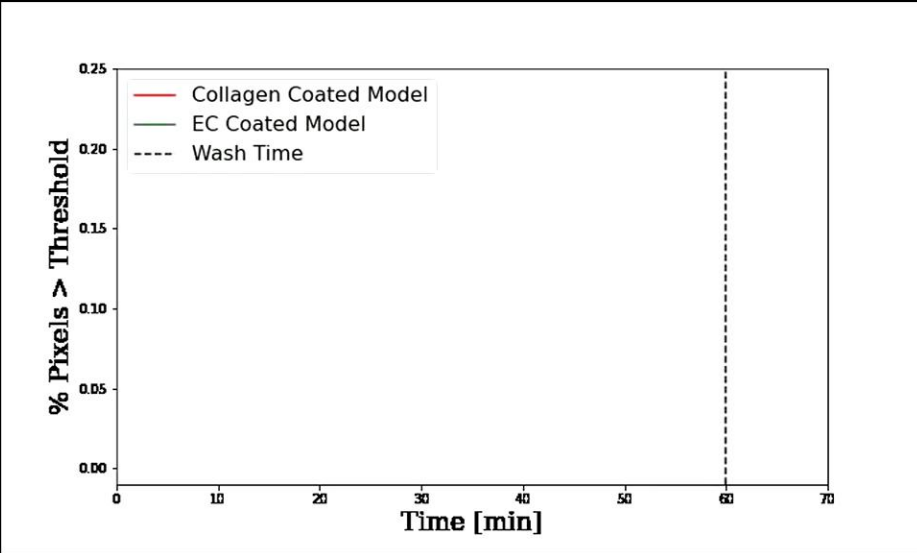


Biophysical based AAA targeting and Cyclophilin A (CyPA)

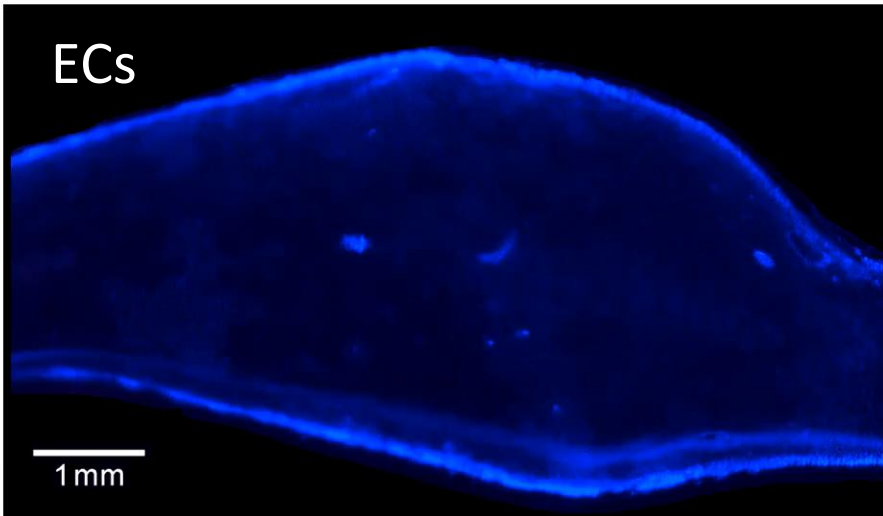
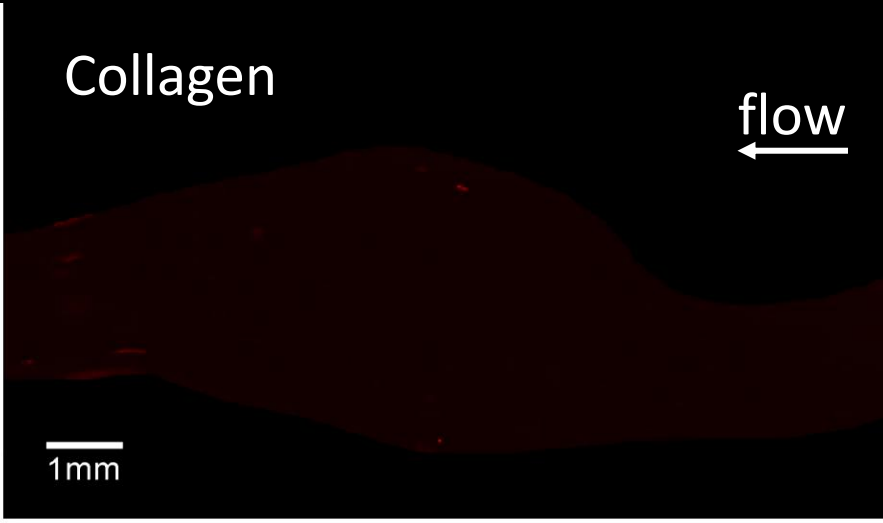


GPVI particles targeting AAA under flow

Fluorescence Intensity vs. Time

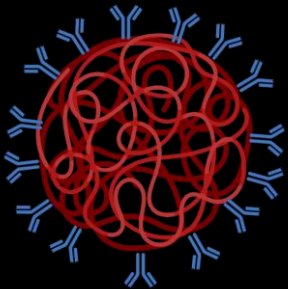


Speed: x250

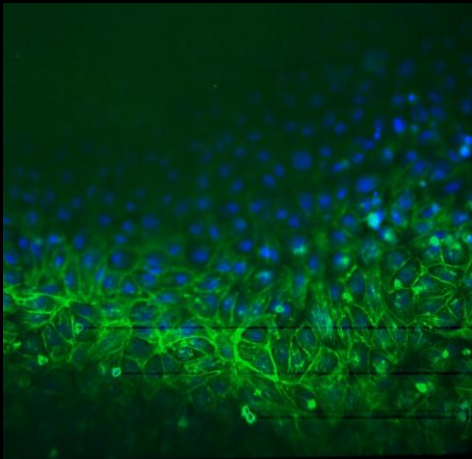


In blue- DAPI In red – GPVI coated Microparticles

➤ Constant flow

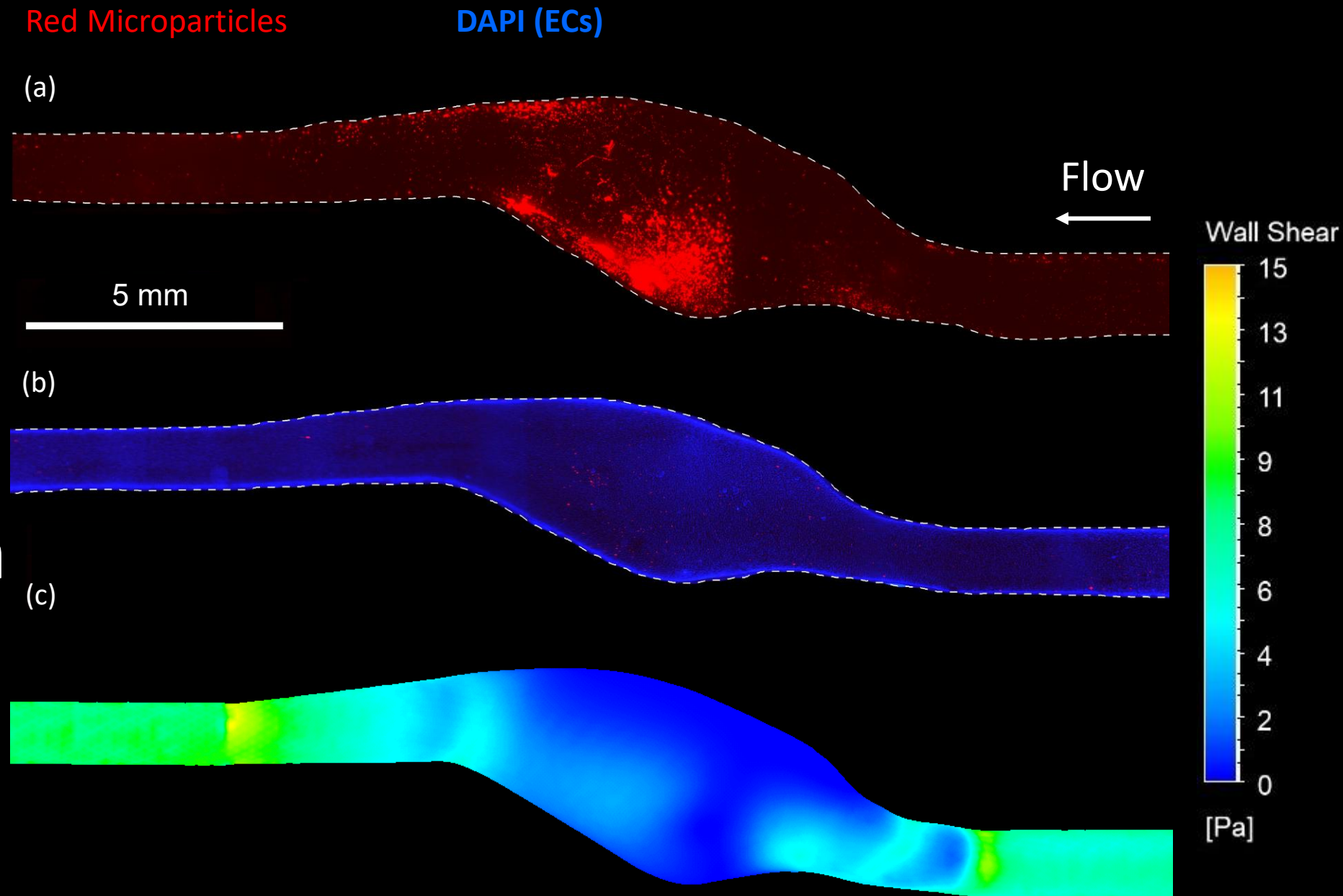


2 μm polystyrene (PS)
GPVI particles



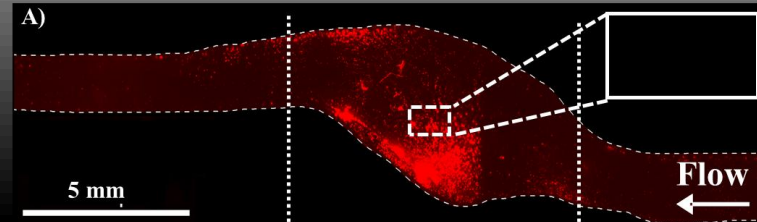
In green –actin
staining

Post Flow Particle Accumulation

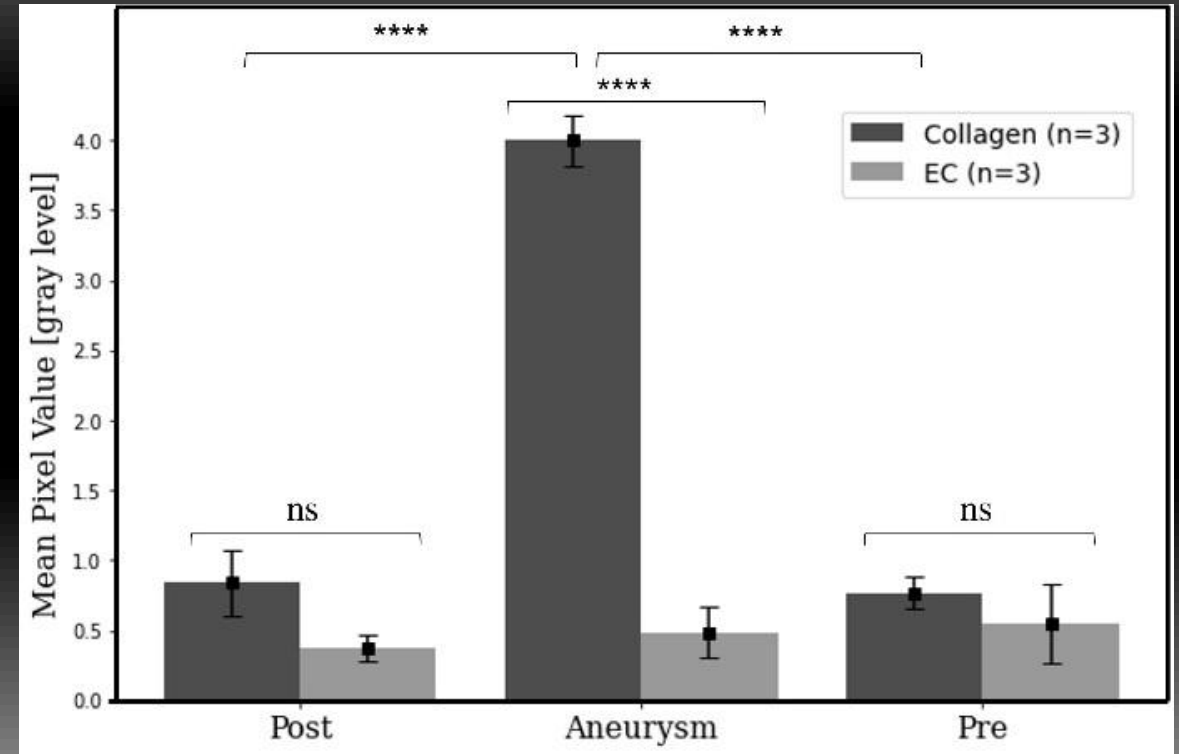
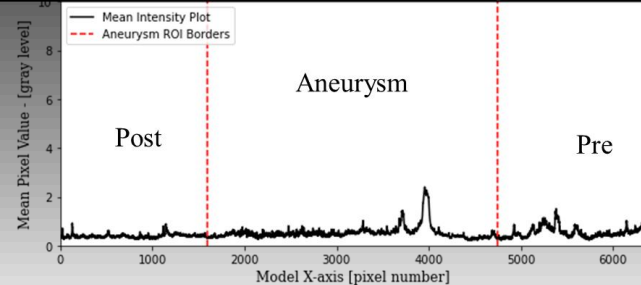
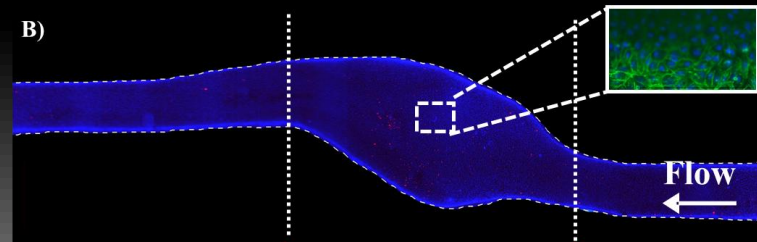


GPVI particles targeting AAA under flow

Collagen

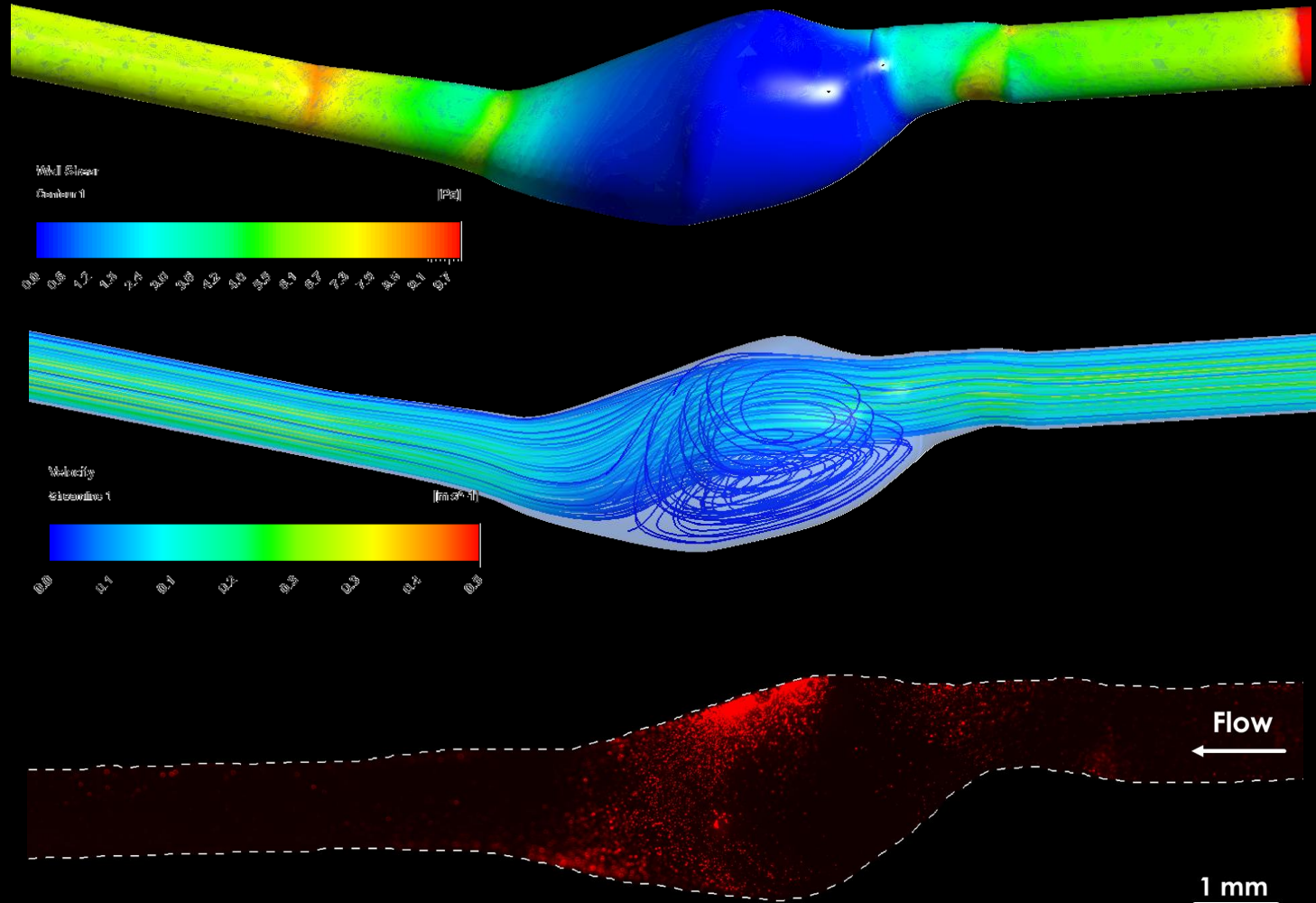


Endothelial
Cells



GPVI particles targeting AAA under flow

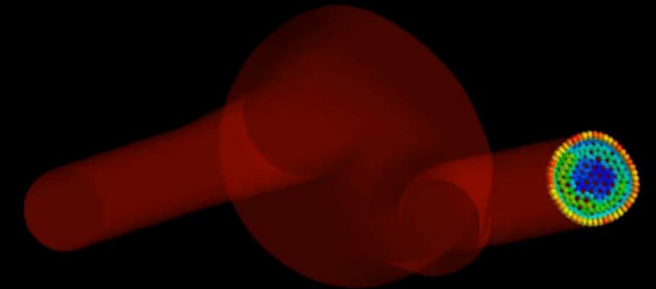
In Vitro mouse model Particle Deposition vs. CFD Simulations



Mouse - Side



Mouse - Front

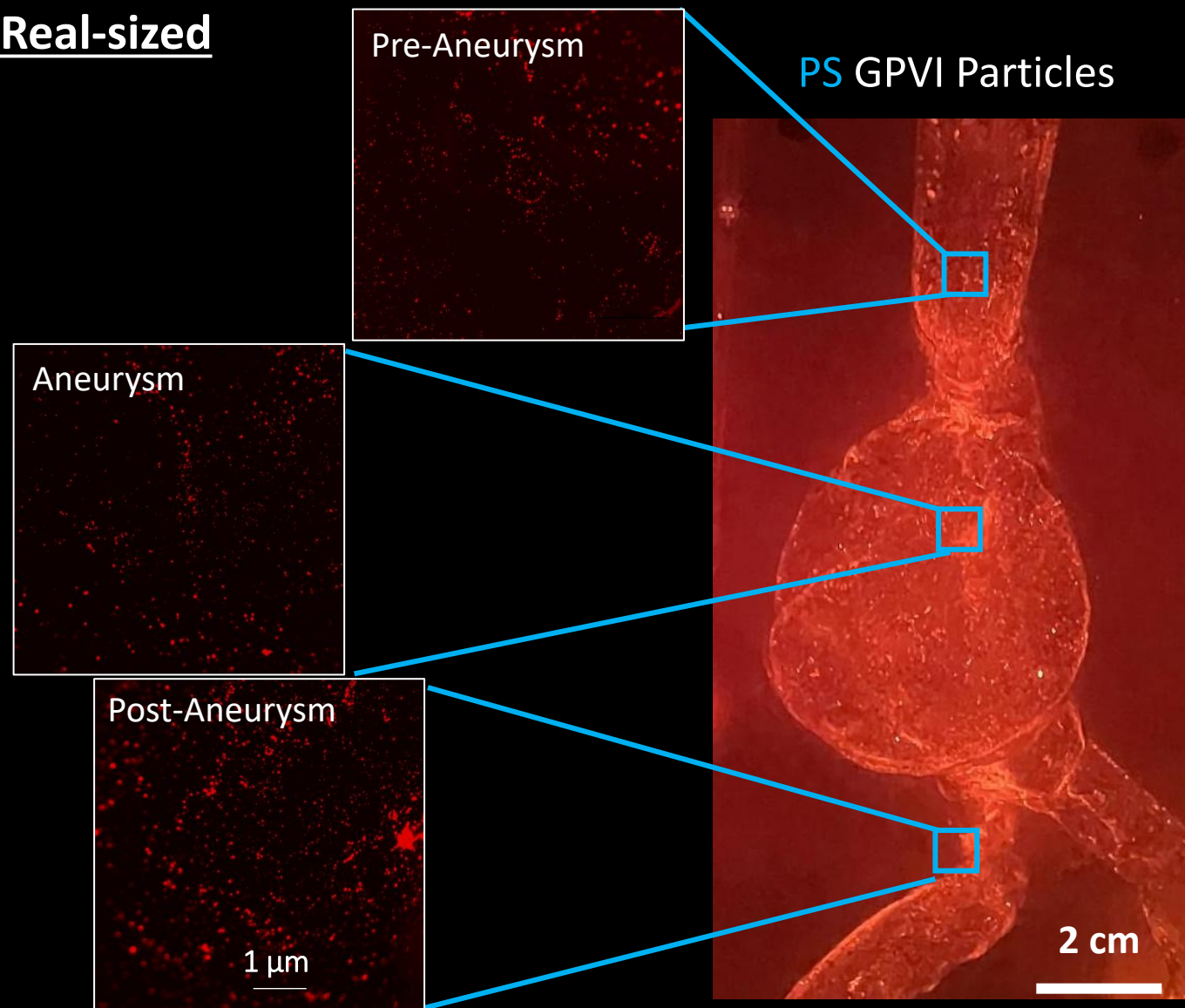


2 μm GPVI Particles $\rightarrow$ Aneurysm Targeting in **mouse** model

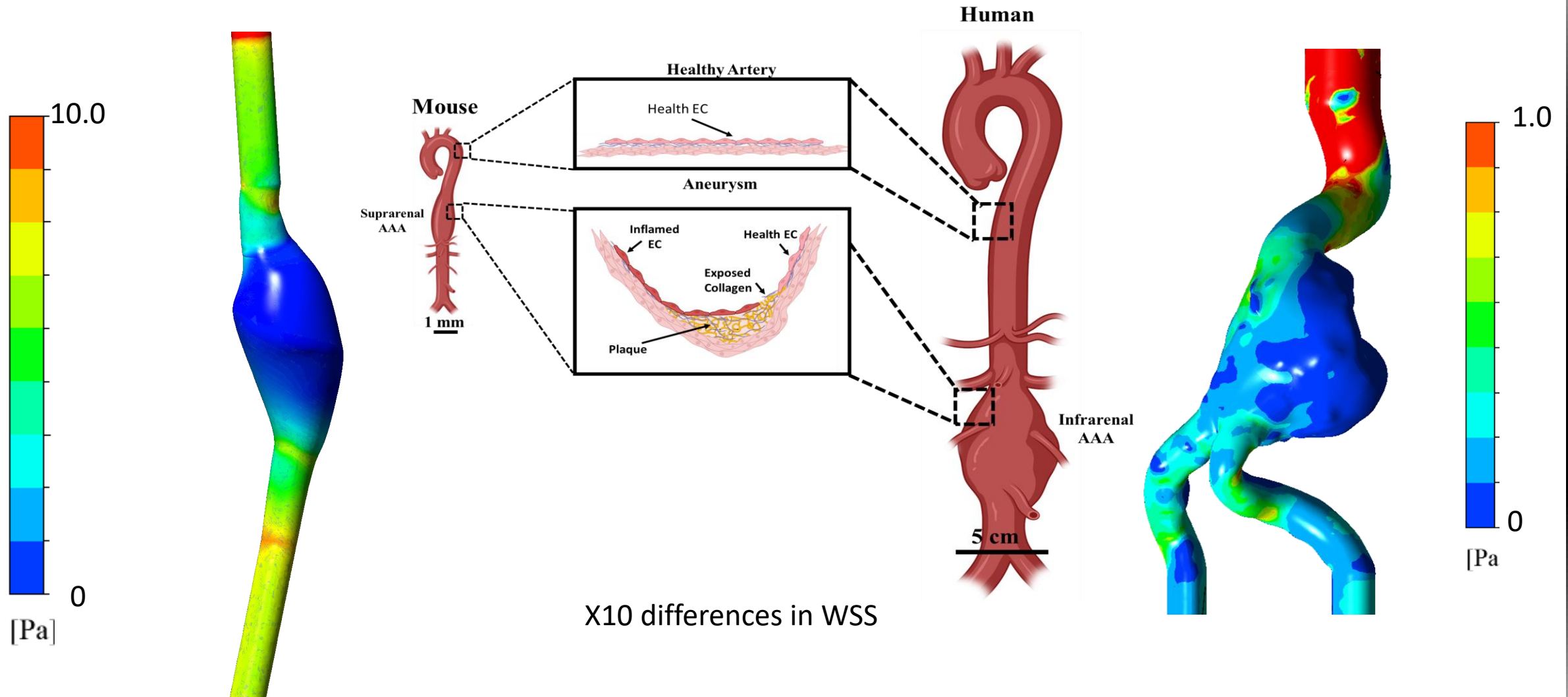
PS GPVI particle targeting in a Human AAA model

In vitro Model Fabrication – Transparent 3D Real-sized Model

Transparent 3D model

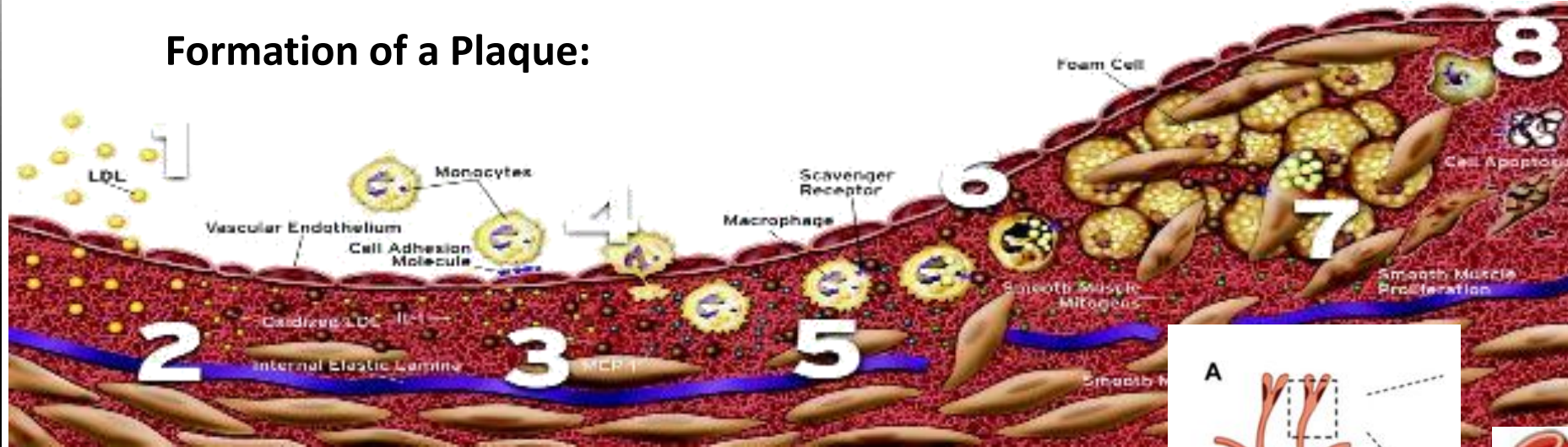


Human vs. Mice AAA

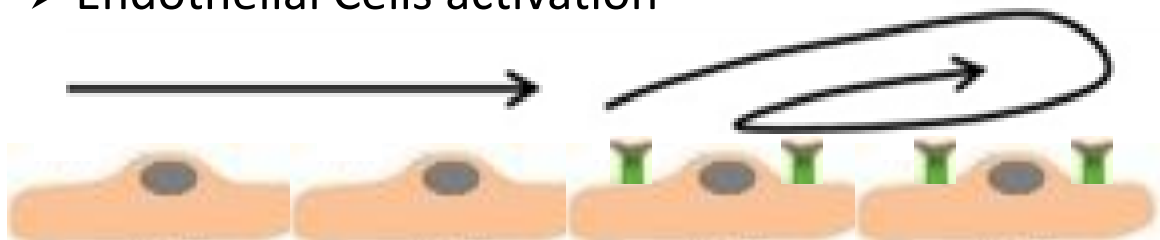


Focal Nature of Atherosclerosis–Role of Hemodynamics

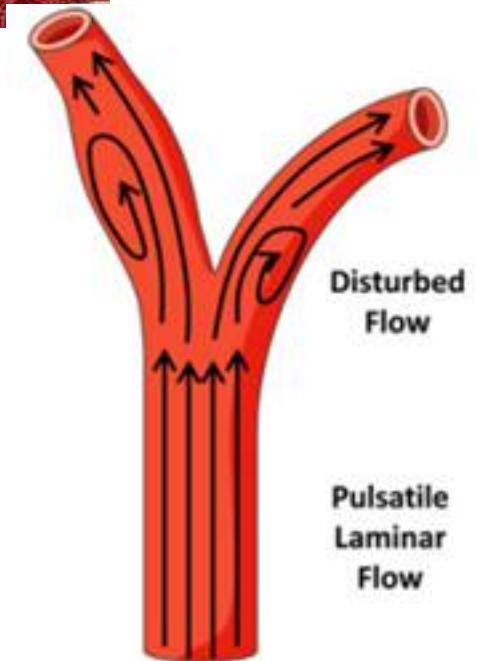
Formation of a Plaque:



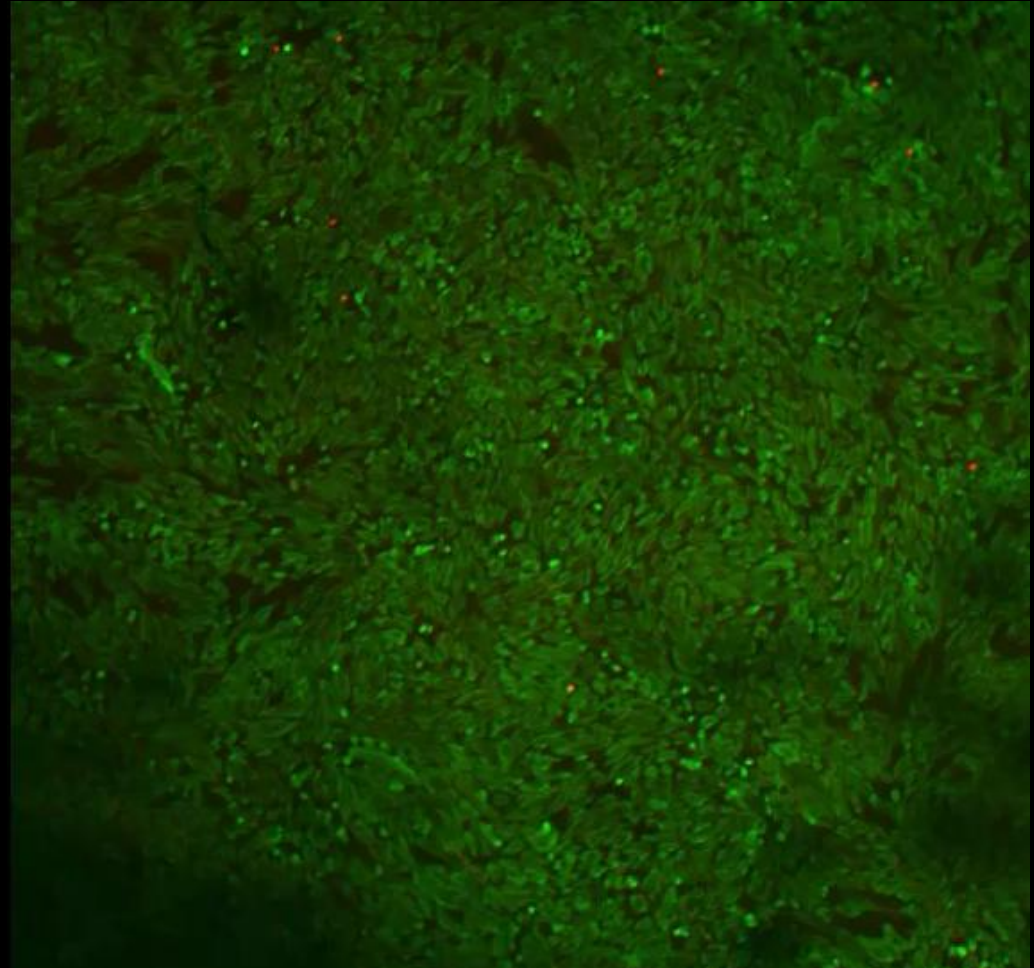
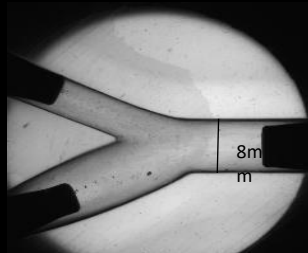
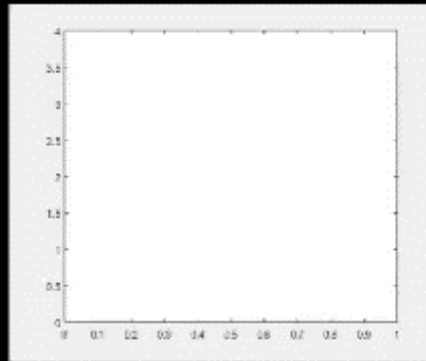
- Atherosclerotic lesions:
 - Tight curves and Bifurcations
 - Disturbed flow
- Endothelial Cells activation



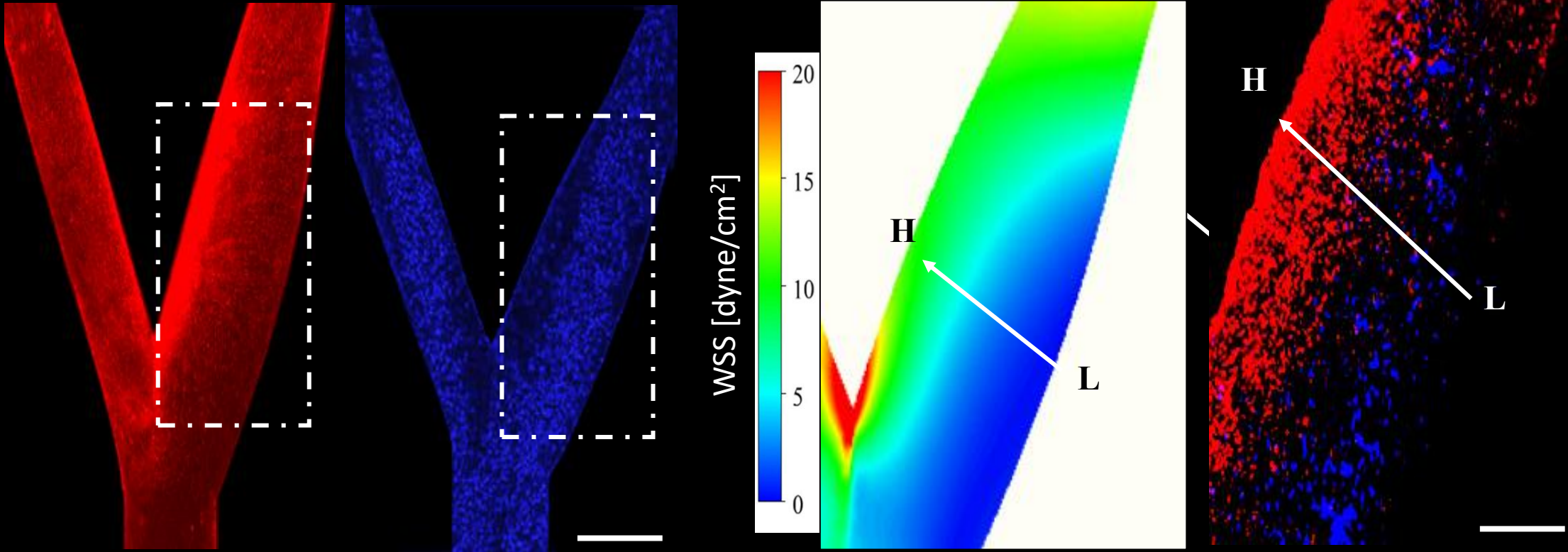
Endothelial Cells



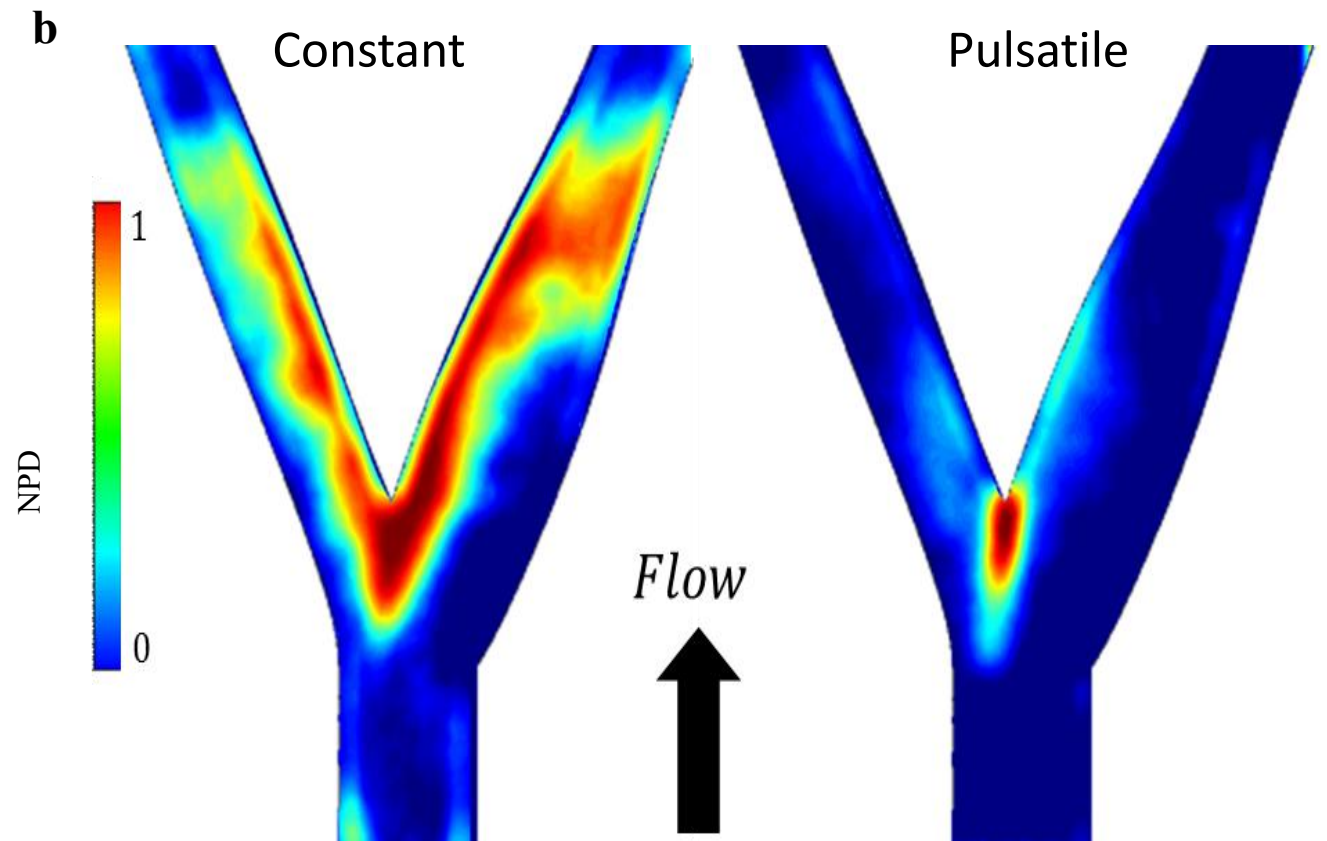
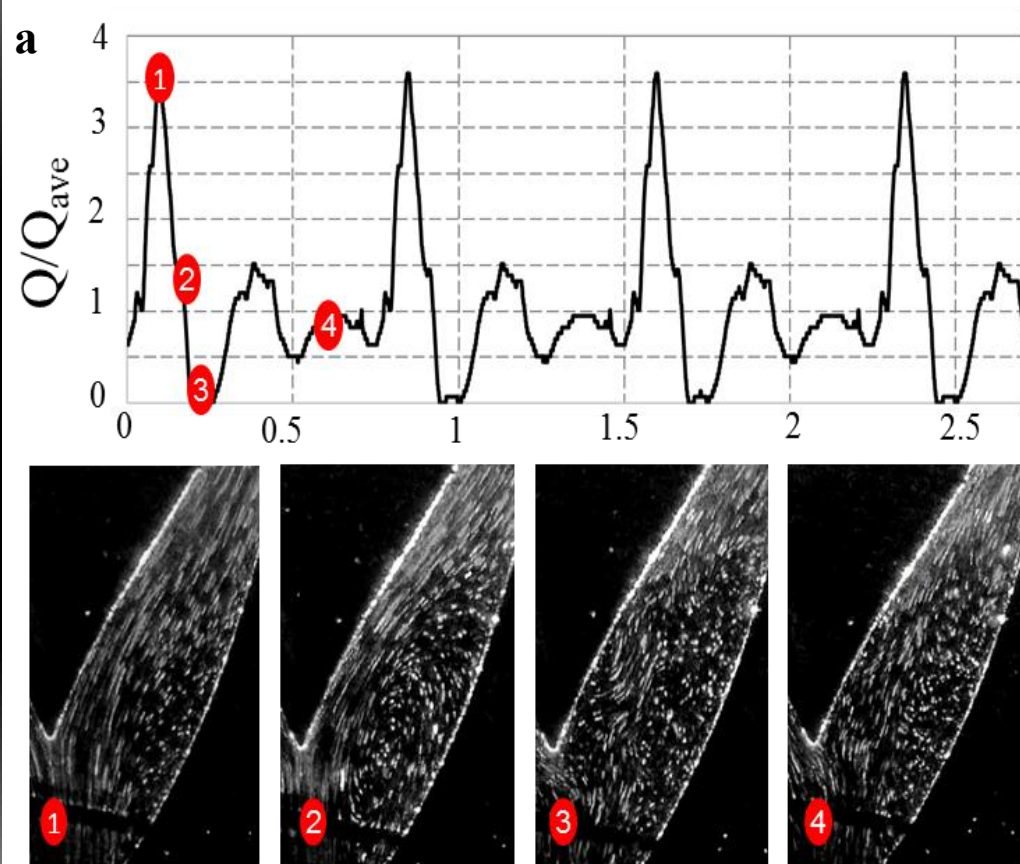
Real Sized Arterial Bifurcation Models



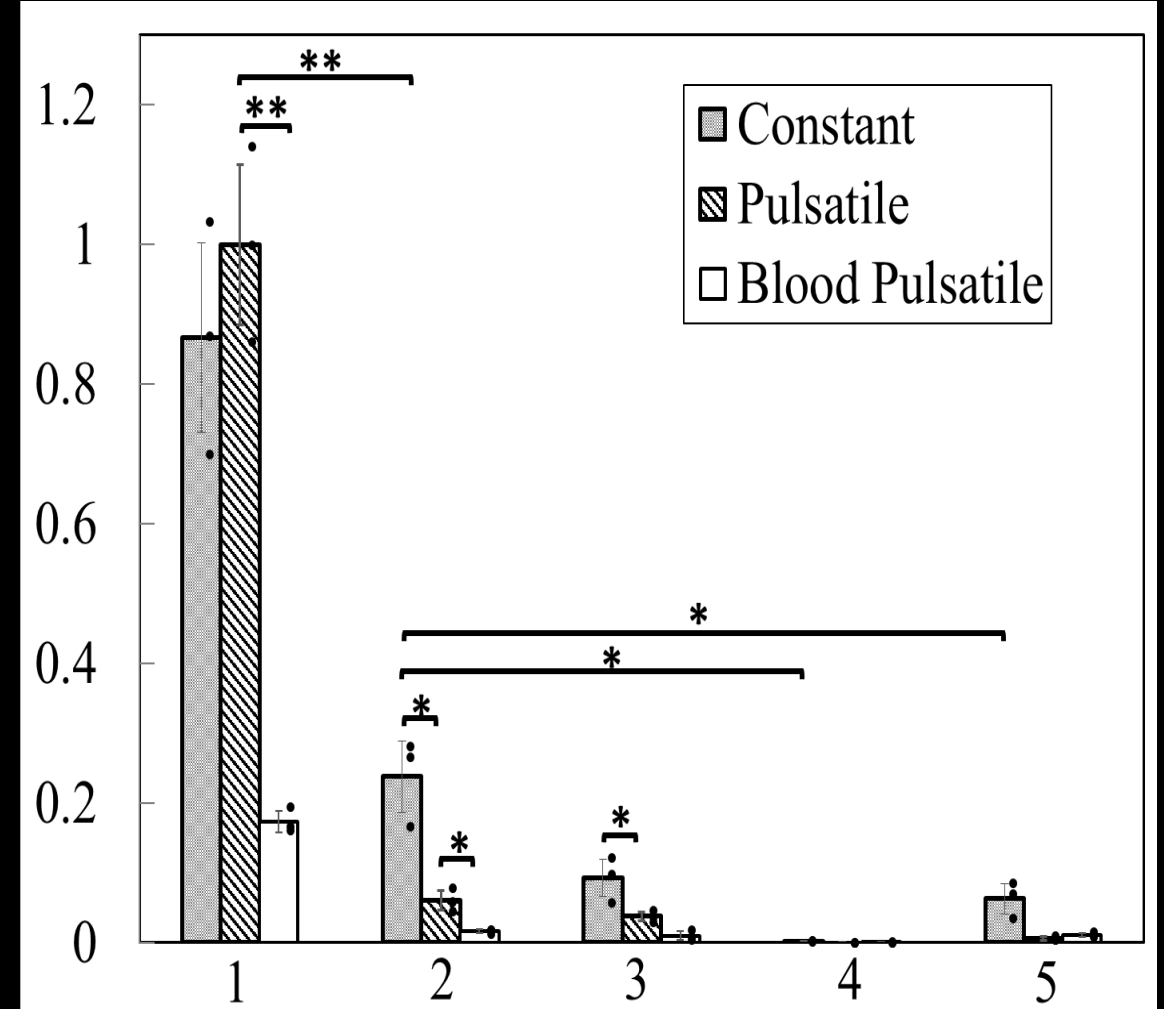
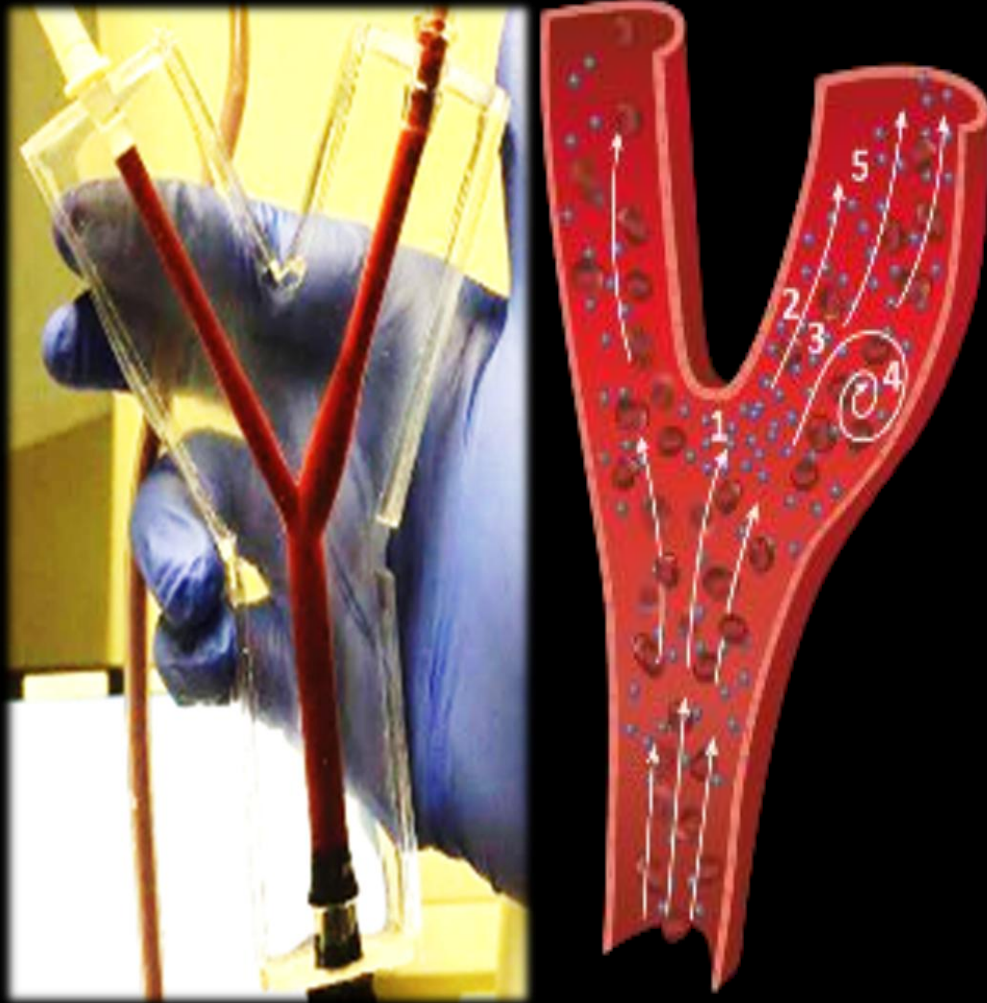
Shear and Flow Structure Dependent Adhesion



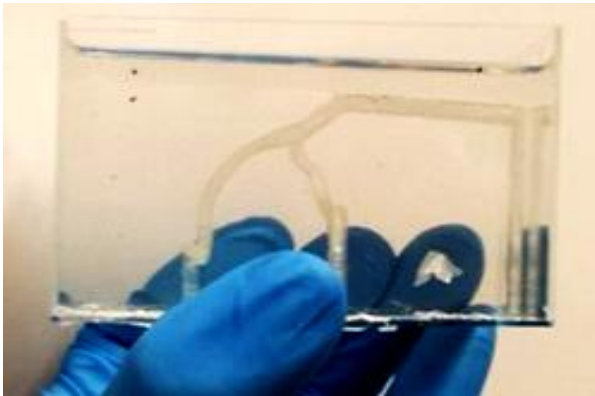
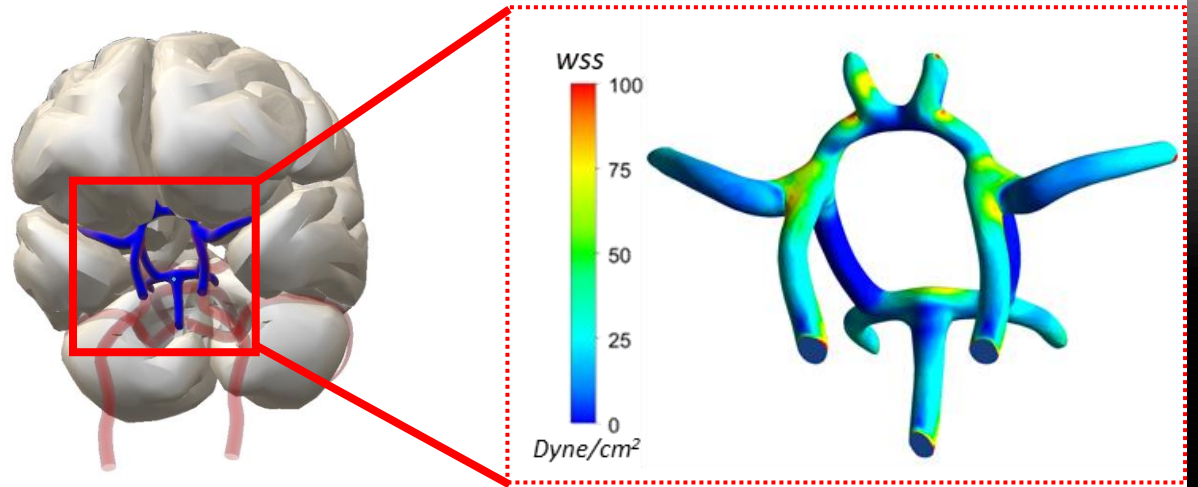
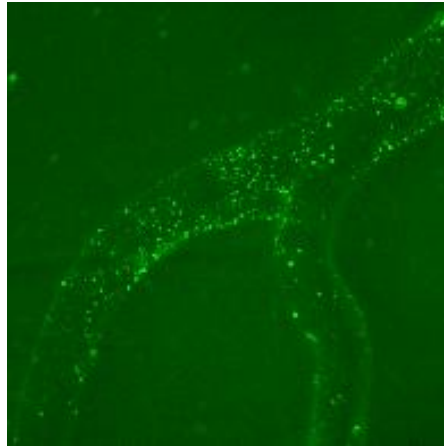
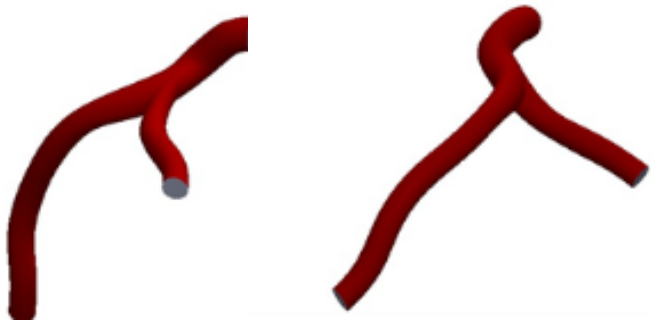
Effect of Pulsatility



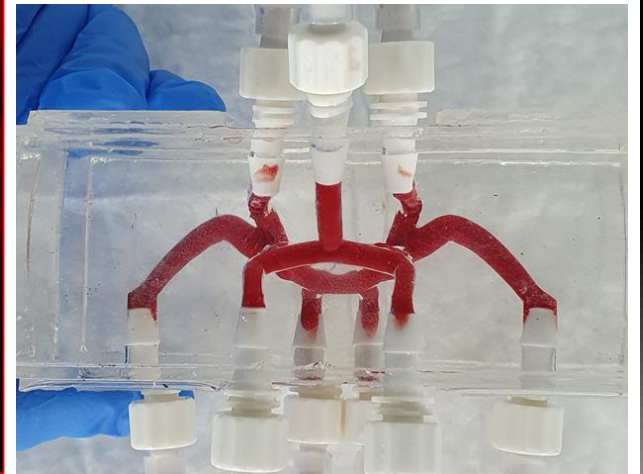
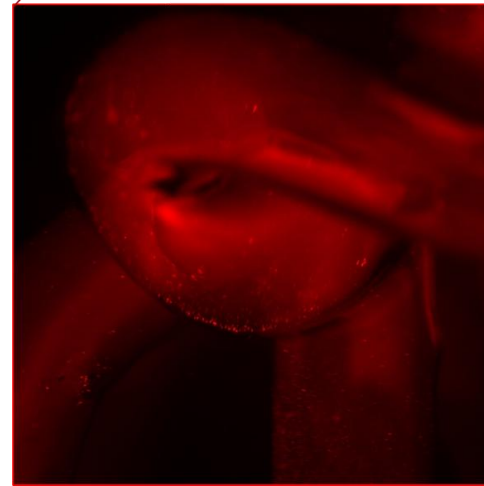
Effect of Pulsatility and Blood on Adhesion



Left Anterior Descending Artery (LAD) and Circle of Willis Model



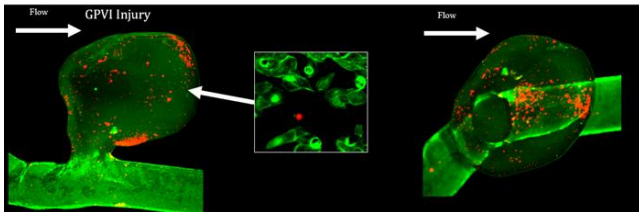
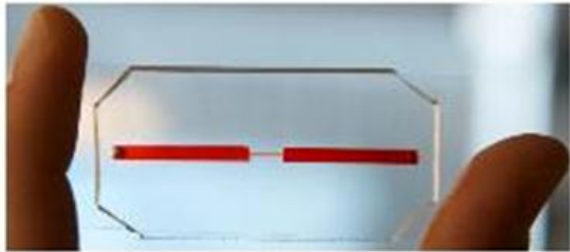
LAD



Circle of Willis

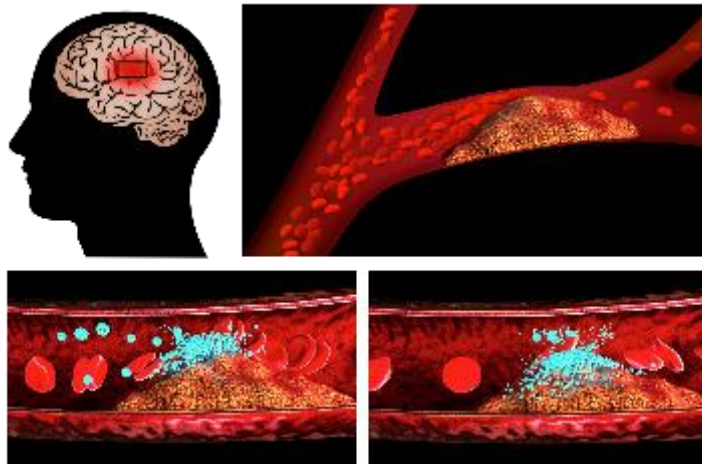
The Bio-physics of Vascular Disease: Localized Treatments and Technologies

In Vitro Dynamic Disease Models



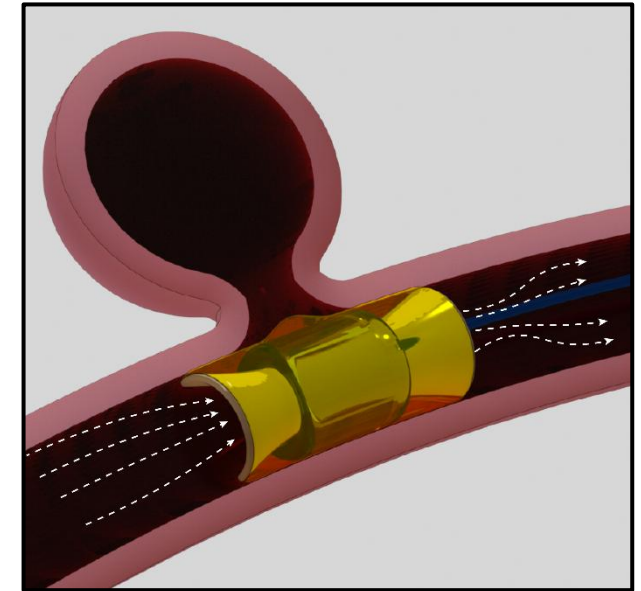
Korin et al., Science, 2015
Epshtein et al., BioTM, 2021

Targeted Drug Delivery/ Nanomedicine



Korin et al. ,JAMA Neurology, 2015

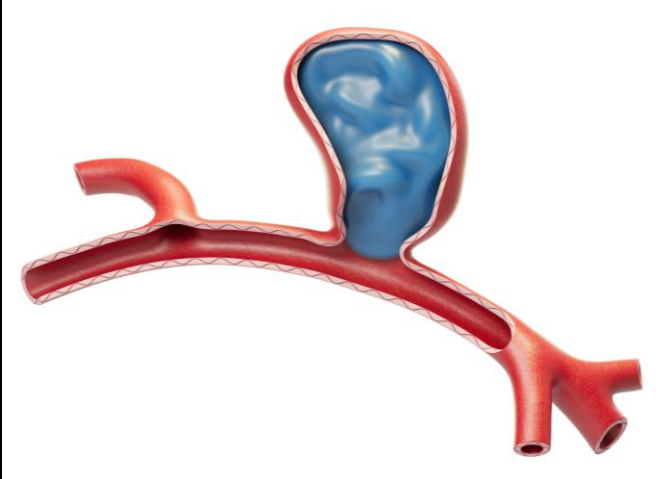
Intraarterial Treatment of Large Vessels/**Devices**



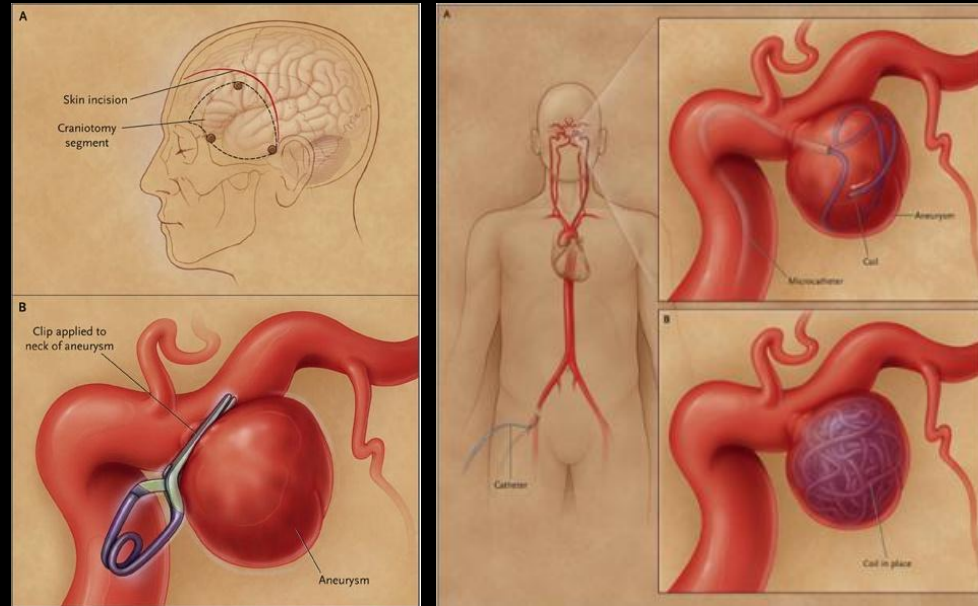
Cerebral aneurysms

Current Available Treatment:

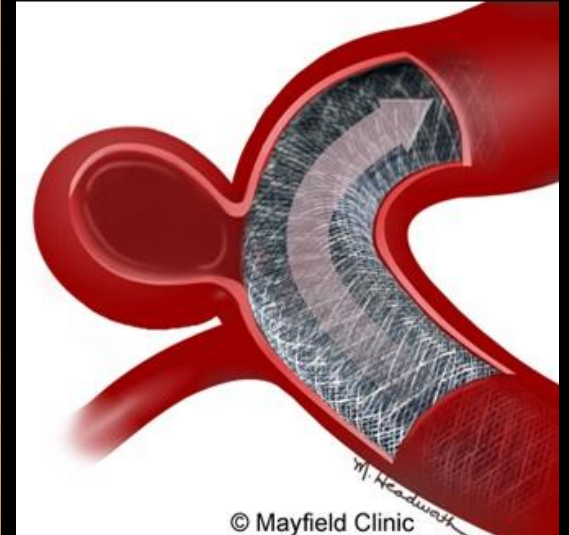
- Clipping
- Coiling
- Stenting and flow diverting



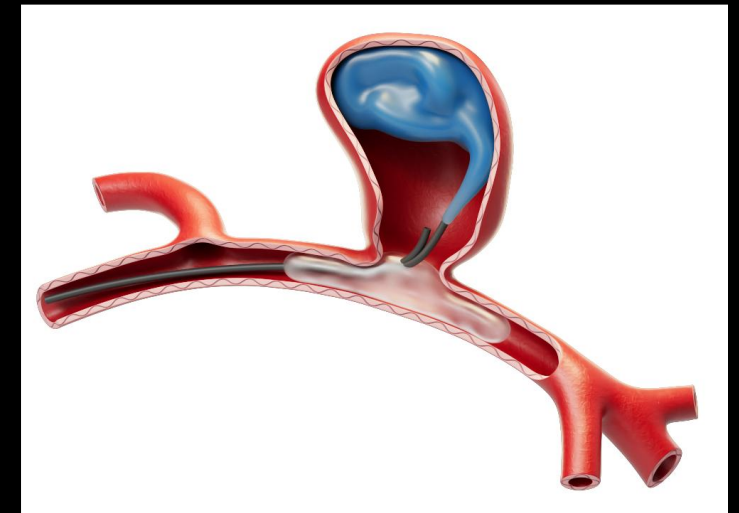
**Biodegradable
Injectable Embolic Agents**



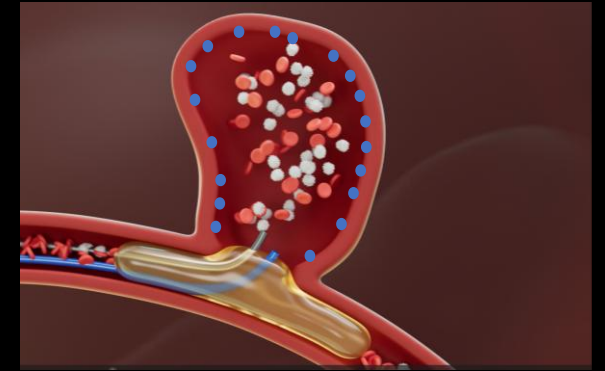
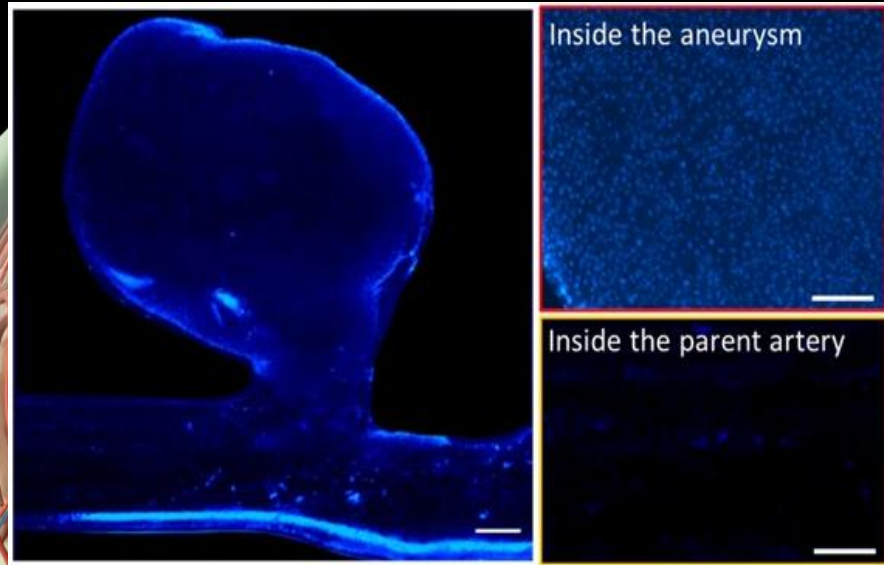
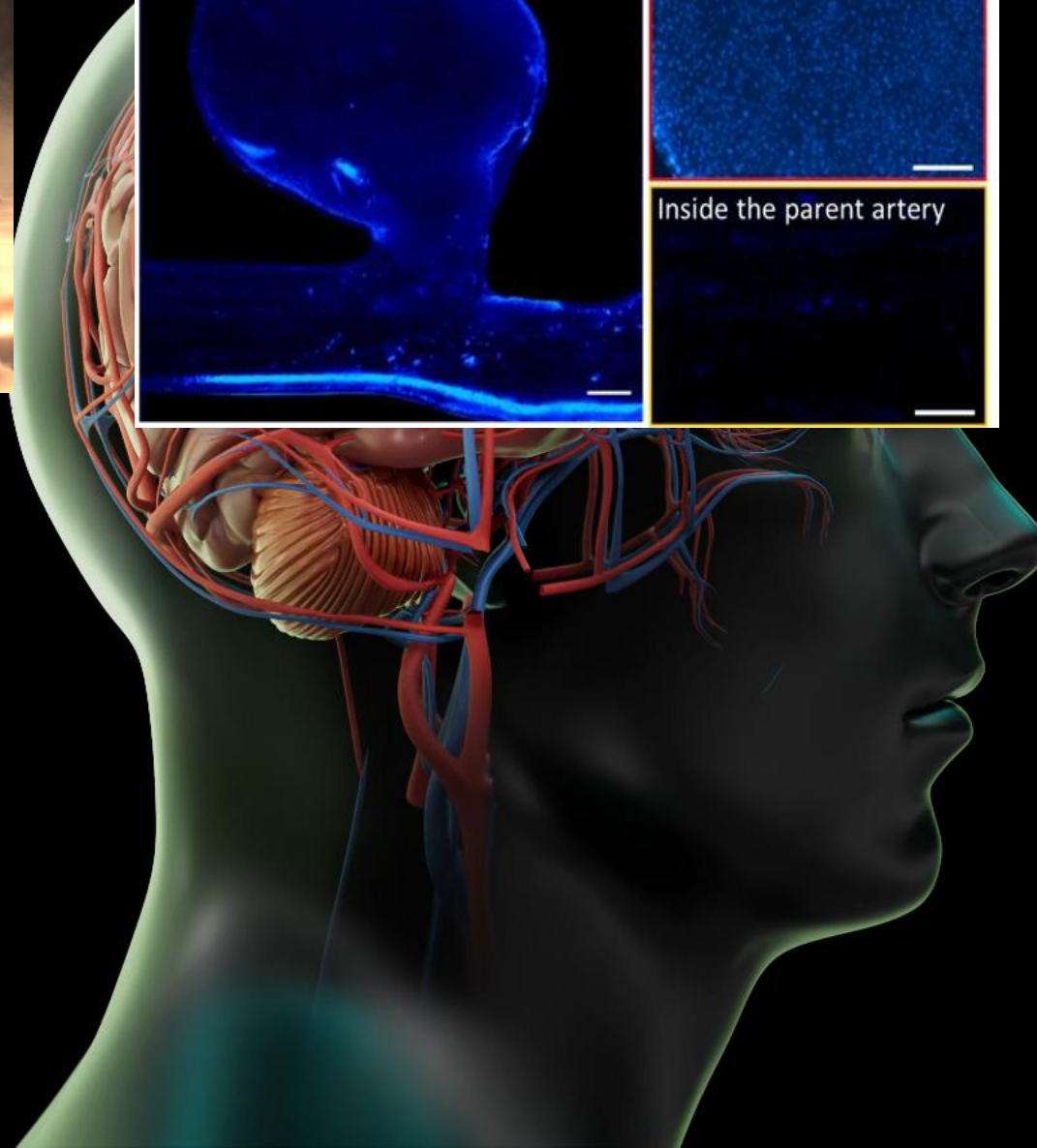
flow diverter



Pressurized Ballon



Fluid Trapping



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Reconstructed Human Patient Dynamic Models for Engineering Targeted Therapeutics for Aneurysms

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