

# *Theranostics: A holistic and revolutionized regime in cardiovascular medicine*



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# Location and Feature of Okayama...

**Sunny, Mild Climate, Historical city & Nice food**





# Research Collaborations

- ✓ Memorandum of Understanding (MoU)
- ✓ Research collaborations
- ✓ Co-supervision of postgraduates
- ✓ Joint paper publications



**Prof. Eiji Matsuura**  
Okayama University

Adjunct Professor  
SUT at Melbourne  
Adjunct Professor  
SUTSUT at Sarawak



**Dr. Rani Sauriasari**  
Universitas Indonesia



**Dr. Alan Yean Yip Fong**  
Sarawak General Hospital



**Dr. Hwang Siaw San**  
Swinburne Sarawak



**Prof. Mrinal Bhawe**  
Swinburne Melbourne

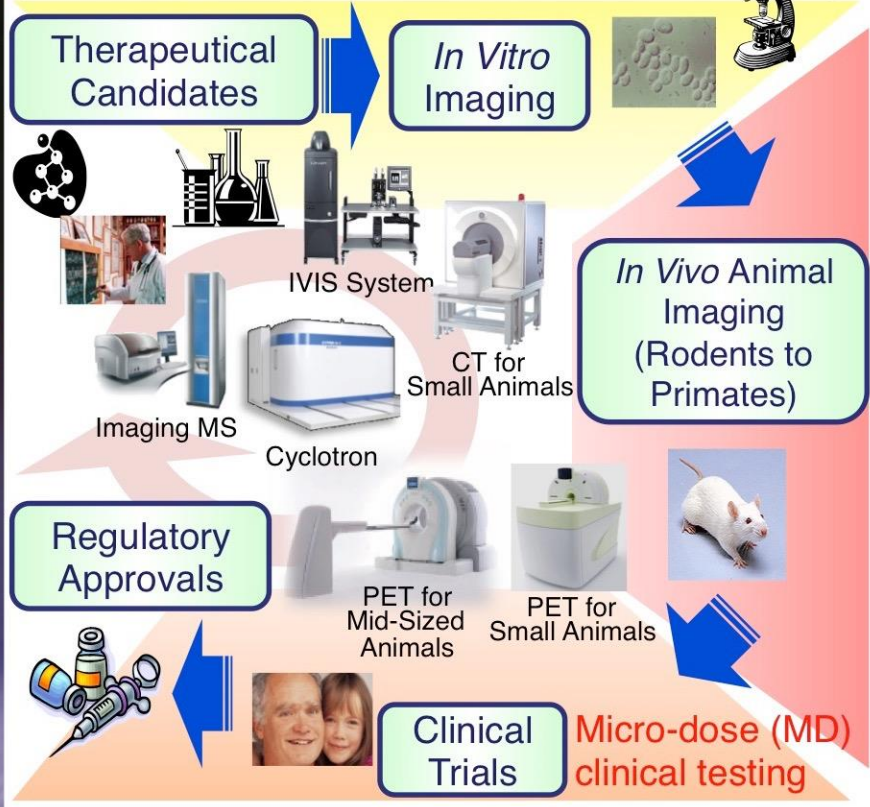


**Prof. Yosry Morsi**  
Swinburne Melbourne

# Okayama Medical Innovation Center (OMIC)

The **OMIC** is the latest animal molecular imaging center in Japan that realizes medical innovation as a key element

**Translational Research (Basic to Clinical Studies)**



**Development of Medical Devices for Both Diagnosis and Therapy**

① **Synthesis/Labeling Technologies of PET Probes**

[Antibody Engineering] Humanizing/Shortening, and Labeling

Focuses centered on atherosclerosis, cancer, and brain diseases

Development of DDS for Theranostics

② **Support Basic to Clinical Studies with Molecular Imaging Technologies**

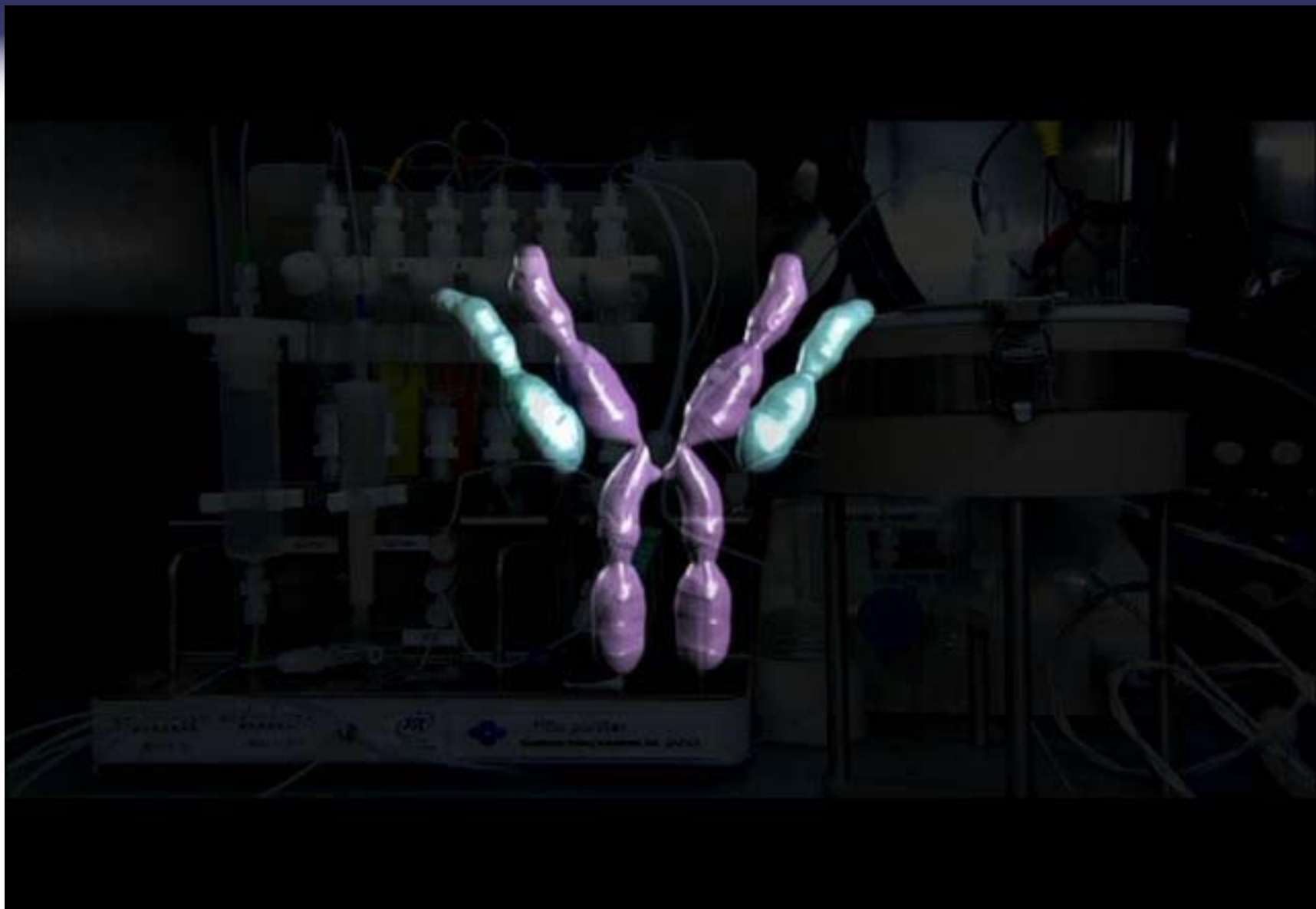
**GMP facilities**

Micro-dose (MD) clinical testing

**PK/PD studies**



# Concept of Antibody Labeling with $^{64}\text{Cu}/^{89}\text{Zr}$





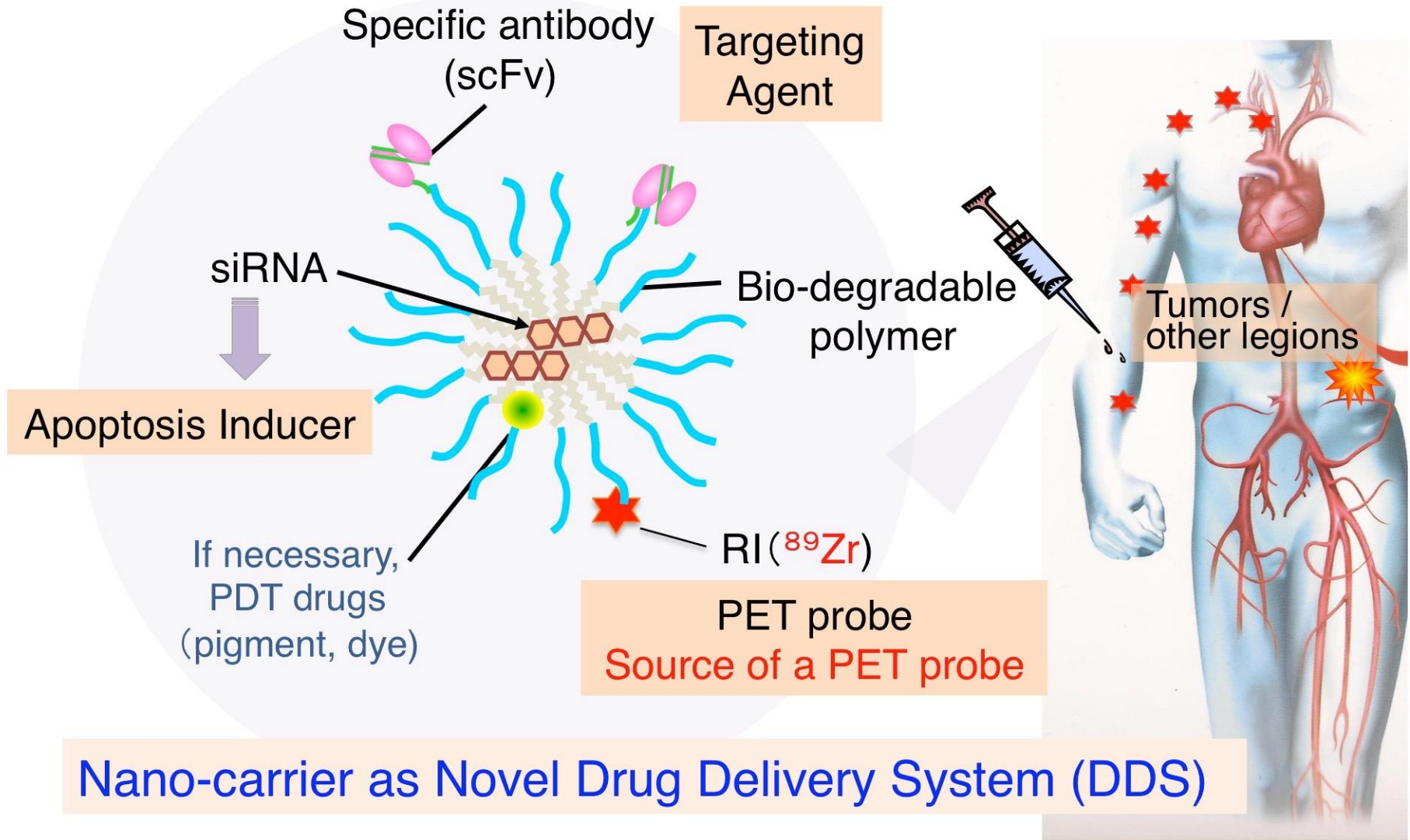
# *Harnessing Disease-specific Autoantibody And Its Variant in Theranostics Of Disease*

☞ The term **“Theranostics”**, is an innovative concept of medical modality featuring a portmanteau of therapeutic and diagnostic systems, was coined in 2002 and has since undergone progressive development into current preclinical stages.



# “Theranostics (Therapy + Diagnostic)”

(Targeted medicine; a platform combining both therapy and diagnosis for disease stratifications)





# Antiphospholipid syndrome (APS)

(Autoimmune-mediated atherosclerosis)

## Disease concepts

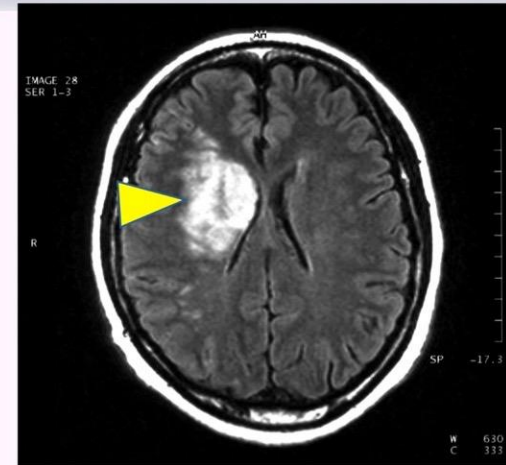
- Thrombotic autoimmune disease
- Caused by a set of autoantibodies, so called “antiphospholipid antibodies (aPL)”

## Clinical criteria

- Arterial and/or venous thrombosis
- Pregnancy morbidities

## Autoantibodies

- Anti-cardiolipin antibodies → X
- Anti- $\beta$ 2-glycoprotein I ( $\beta$ 2GPI) antibodies
- Lupus anticoagulants → ???



Stroke



DVT



# β<sub>2</sub>-Glycoprotein I (β<sub>2</sub>GPI)

(A major target antigen of antiphospholipid antibodies)

Reprinted from THE LANCET, July 21, 1990, pp. 177–178

## Anticardiolipin cofactor(s) and differential diagnosis of autoimmune disease

SIR,—At the 4th International Symposium on Antiphospholipid Antibodies, held in Italy in April, 1990, we reported that anticardiolipin antibodies (ACA), obtained from the sera of autoimmune patients, reacted with a complex of negatively charged phospholipids and cofactor(s) derived from normal human sera.<sup>1</sup> We can confirm that the anticardiolipin cofactor(s) we reported is identical to Dr Galli and colleagues' "ACA-cofactor" (June 30, p 1544).

We purified a cofactor by cellulose column chromatography and affinity chromatography using columns conjugated with protein A

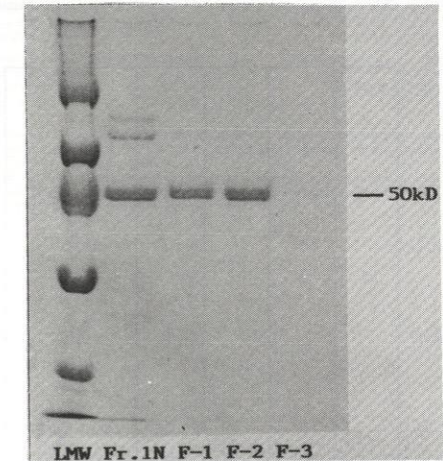
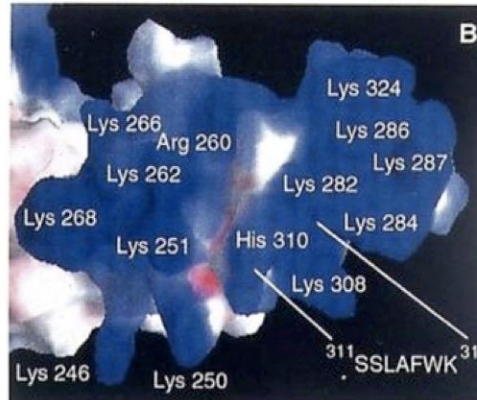
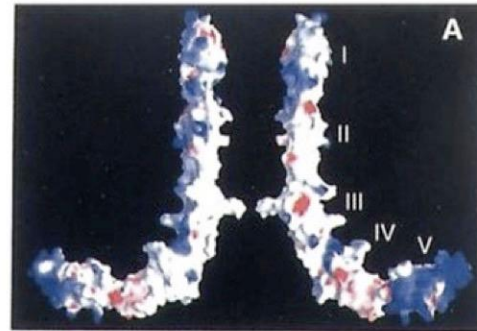
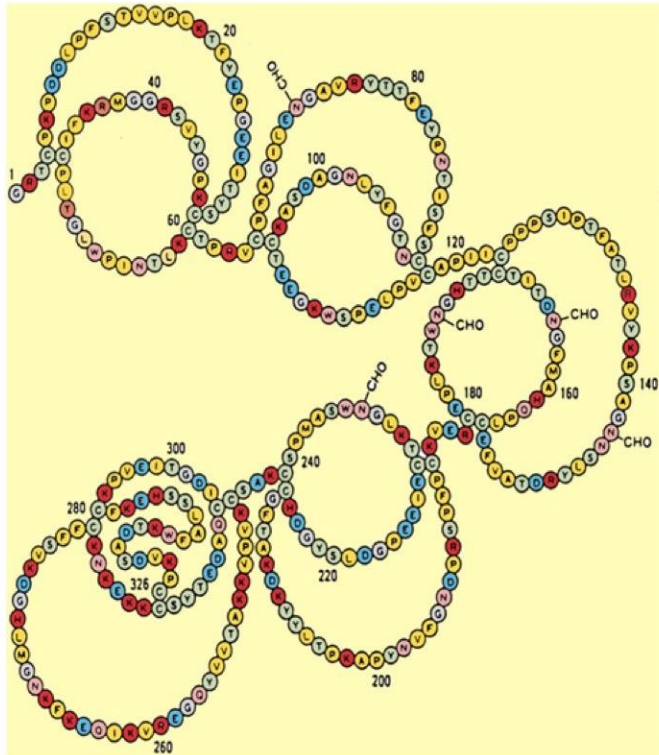


Fig 1—Analytical electrophoresis on SDS-polyacrylamide gel of human anticardiolipin cofactor(s).

LMW=low-molecular-weight markers.  
Fr.1N=cofactor(s)-enriched fraction obtained by column chromatography (eluted with 14 mmol/l phosphate buffer, pH7.4) followed by affinity chromatography on columns conjugated with protein A and murine monoclonal anti-human IgG.

F-1 = fraction adsorbed on liposomes composed of cardiolipin.

F-2 = fraction adsorbed on liposomes composed of cardiolipin and dipalmitoylphosphatidylcholine (DPPC) (20:80, mol %).

F-3 = fraction adsorbed on liposomes composed of dipalmitoylphosphatidylethanolamine (DPPE) and DPPC (20:80, mol %). No bands detected.

*Lancet 1990*

Anti-cardiolipin cofactor (mw 50 kDa) *Lancet 1990, Lancet 1991, J Immunol 1992*

cDNA cloning of β<sub>2</sub>GPI's cDNA and its protein primary structure *Int Immunol 1991*

X-ray electron spectroscopy (XPS) provided an idea that the epitopes are cryptic *J Exp Med 1994*

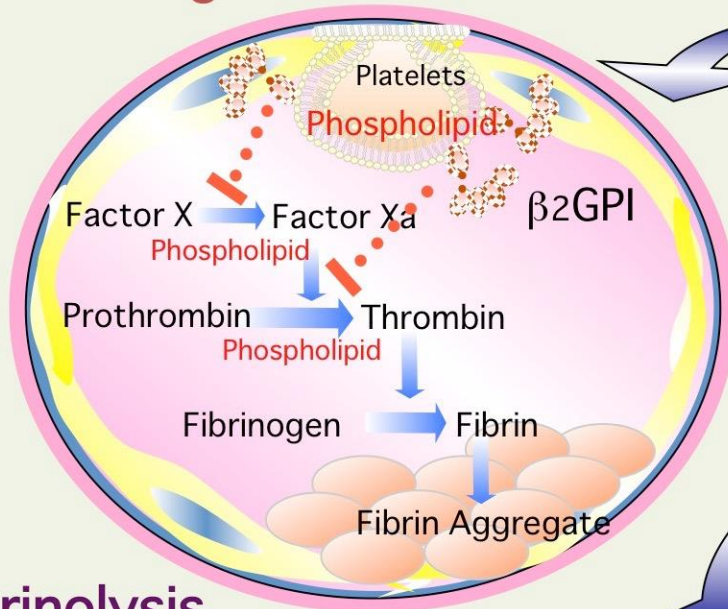
The epitopes characterized with recombinant mutants expressed in baculovirus expression system *Clin Exp Immunol 1993, Blood 1996*

Eiji Matsuura, PhD, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences



# Roles of $\beta$ 2-glycoprotein I ( $\beta$ 2GPI)

## Blood coagulation



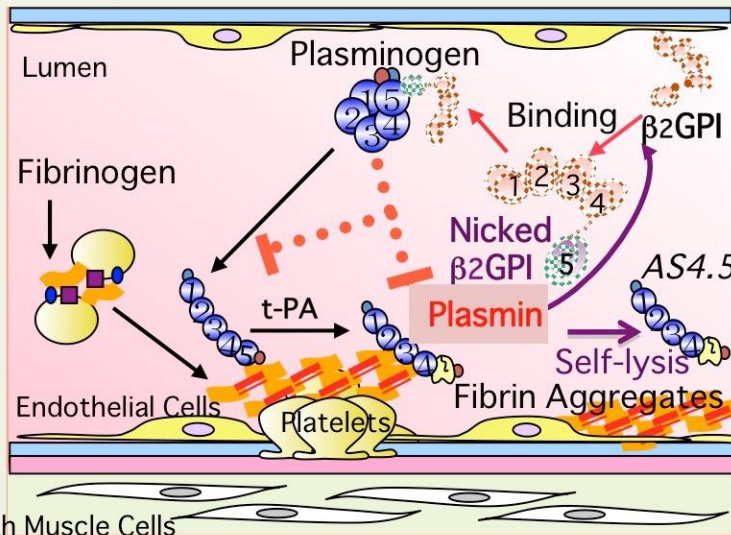
Inhibit



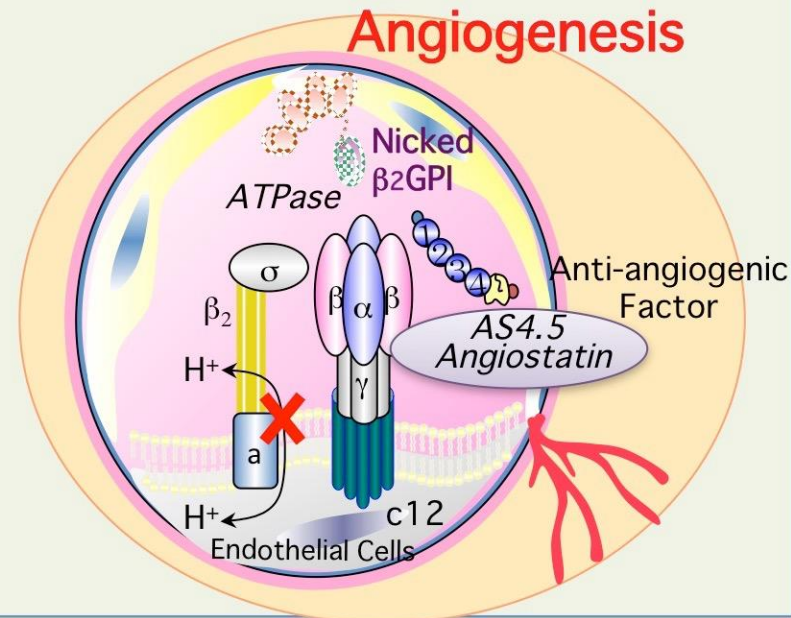
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Inhibit

## Fibrinolysis



## Angiogenesis

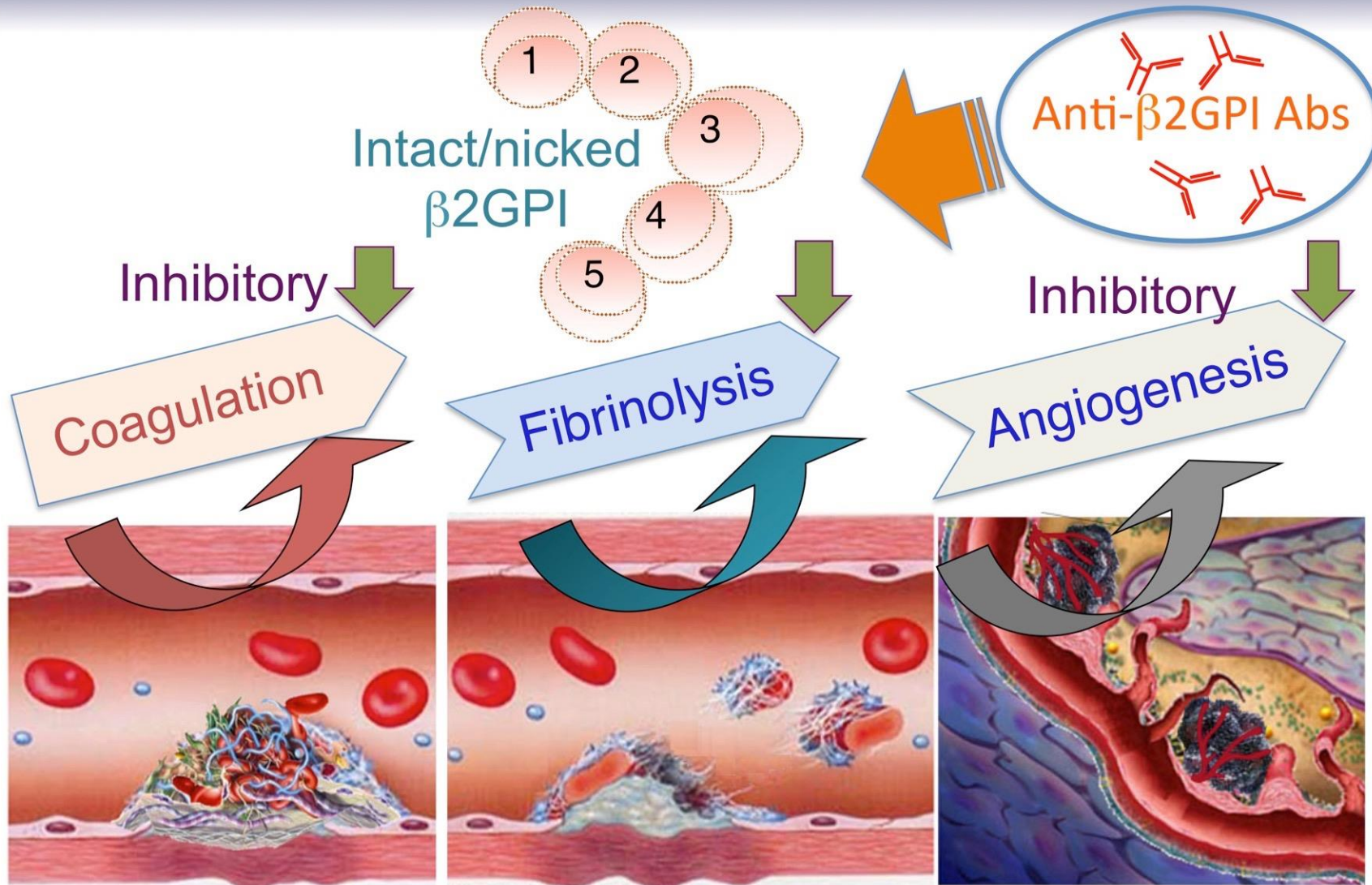


Smooth Muscle Cells





# Regulatory function of $\beta$ 2GPI in haemostasis

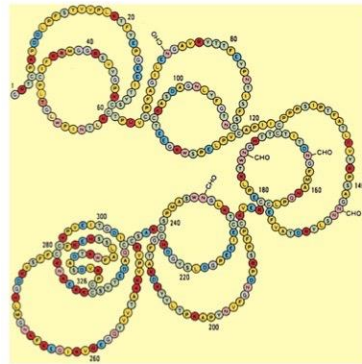




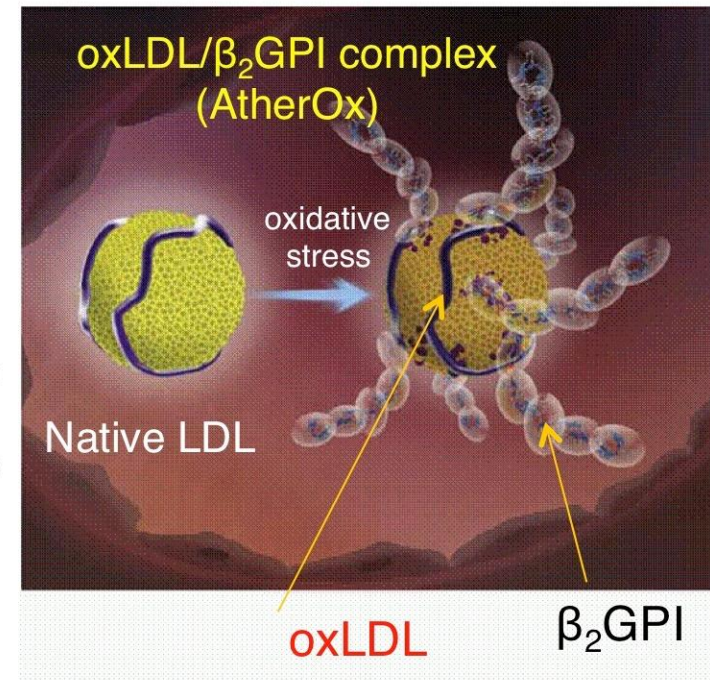
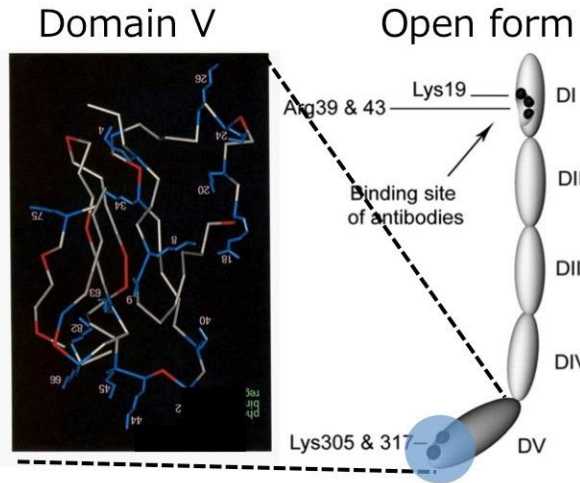
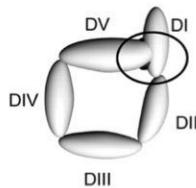
# The AtherOx<sup>®</sup> Technology (for *in vitro* diagnosis & *in vivo* imaging)

**AtherOx:** Complexation of oxidized low-density lipoprotein (oxLDL) and  $\beta_2$ -glycoprotein I ( $\beta_2$ GPI).

Proprietary atherosclerosis biomarker (US Registered trademark)



Circular form



Unique feature: unlike native LDL, oxLDL binds  $\beta_2$ GPI (oxLDL/ $\beta_2$ GPI complexes)

**$\beta_2$ GPI bridges oxidative stress and immunology to atherothrombotic CVD**

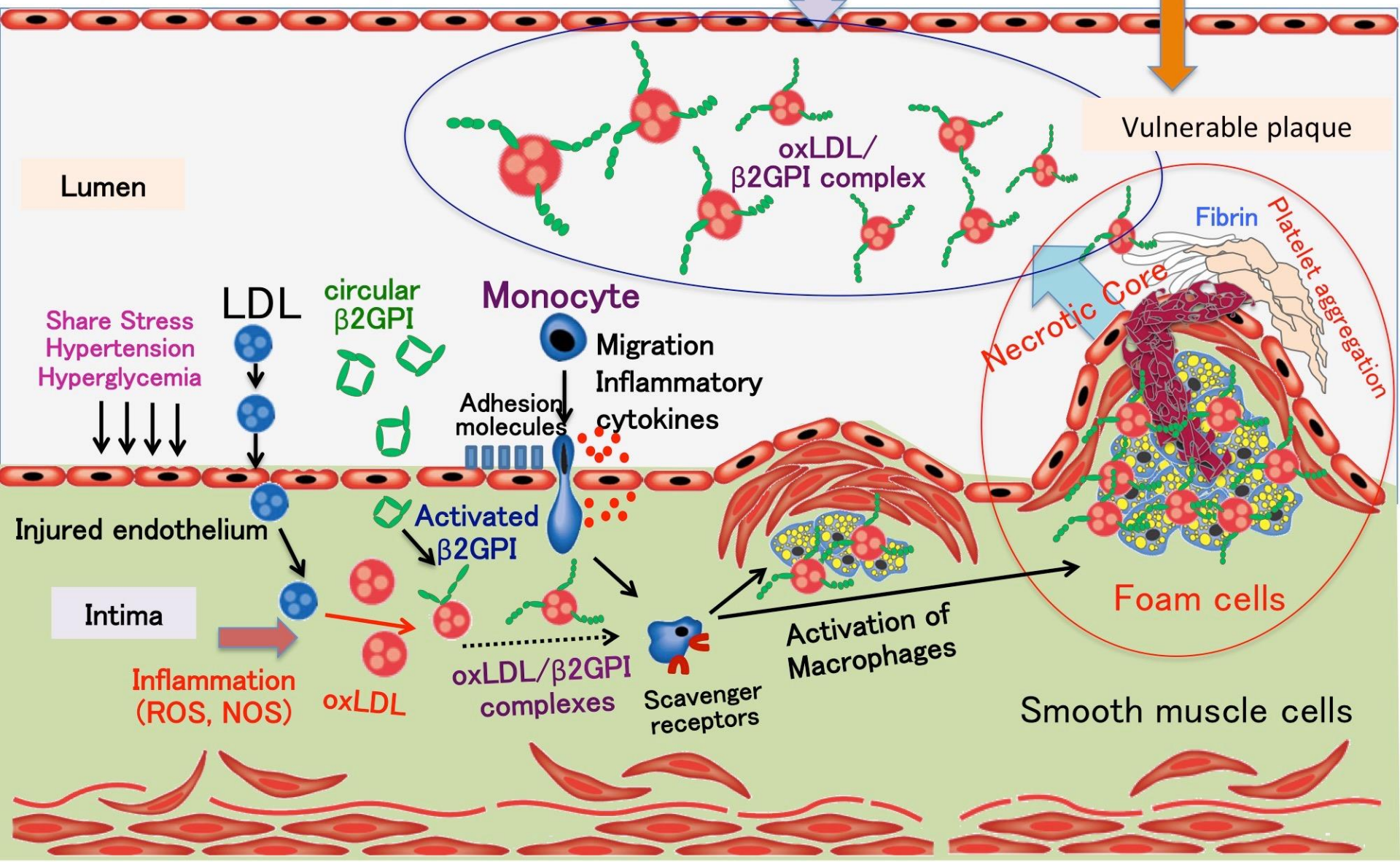




# Paradigm of vulnerable plaque diagnosis

IVD (by AtherOx<sup>®</sup>)

PET imaging

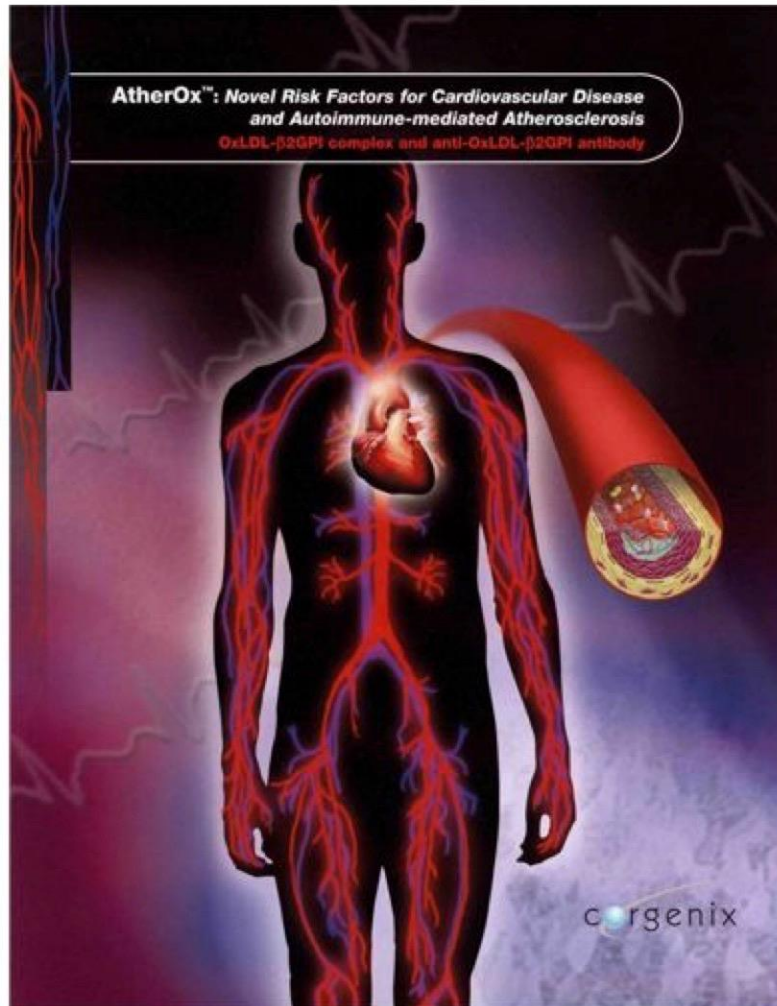




# A diagnostic marker of vascular inflammation

## AtherOx<sup>®</sup> and IgG/IgM Anti-AtherOx<sup>®</sup>

Assay kit for oxLDL/ $\beta$ 2GPI complex and IgG/IgM anti-oxLDL/ $\beta$ 2GPI Abs



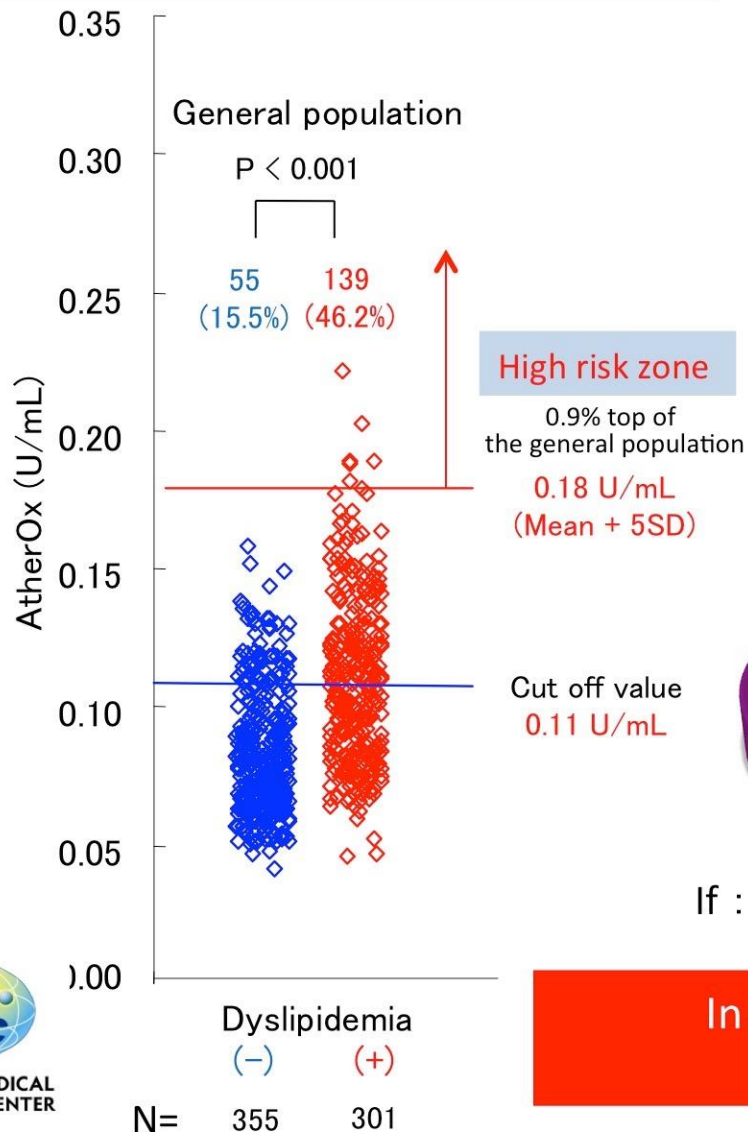
*Related assay kits (now developing..)*  
Human CRP/oxLDL/ $\beta$ 2GPI immune complex  
Mouse SAP/oxLDL/ $\beta$ 2GPI complex



# Prospected number of target-disease population and market size of the PET imaging for LDL- $\beta$ 2GPI complexes (AtherOx<sup>®</sup>)

(By Japanese DGAO-Study)

## DGAO-Study Distribution of AtherOx



## Statistics for the cause of death

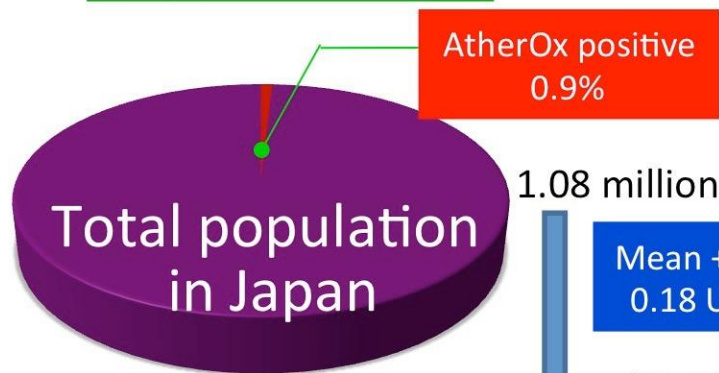


The cause of death with cardiovascular disease accounted for about 30% of all.



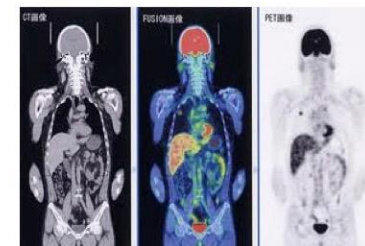
PET-CT

## Prospective market size



If : 600 USD/in vivo PET test

**In vivo imaging market: 6.48 million USD**

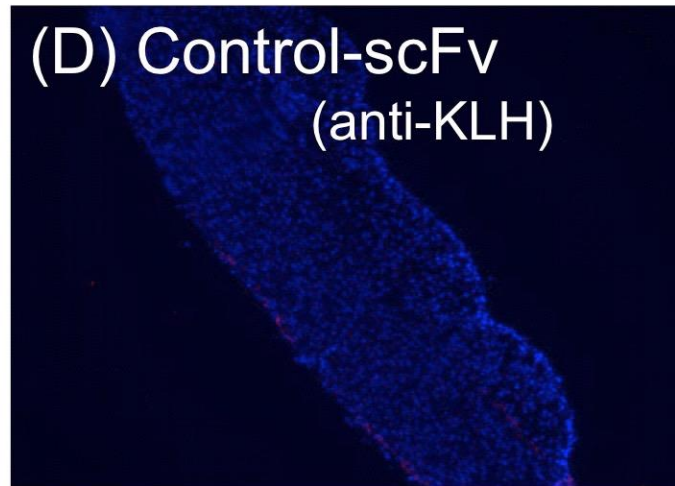
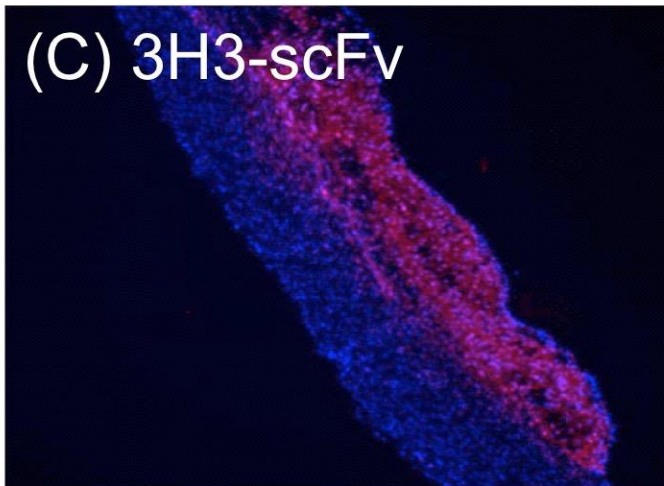


# Specificity of 3H3 scFv (anti-oxLDL/ $\beta$ 2GPI )

*In vitro* study with aorta of the WHHL rabbits



Immunostaining with



3H3 scFv:  
Cy5.5 (in red)

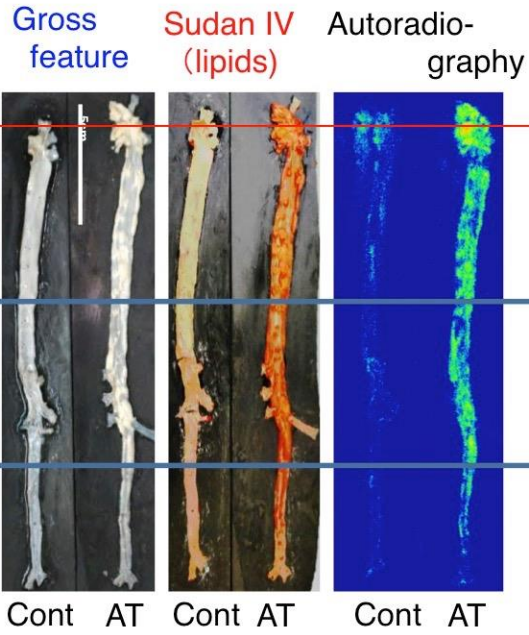
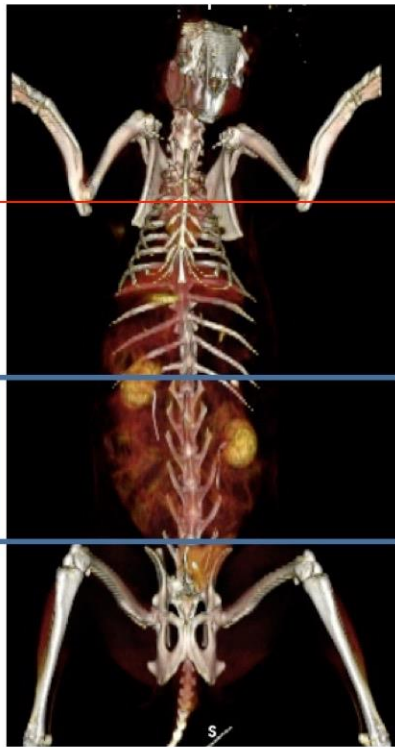
Nuclei staining:  
DAPI (in blue)

I: intima  
M: media.

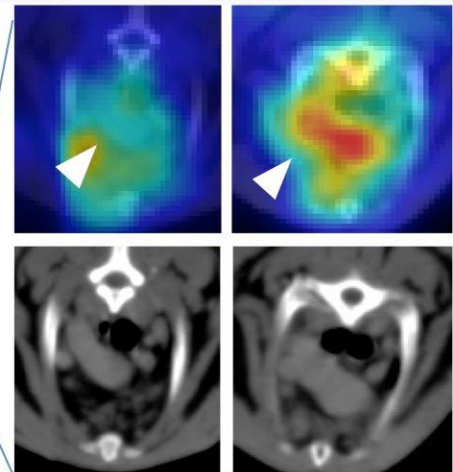


# Summary of PET imaging of atherosclerotic plaques in the WHHL rabbits

CT (angiography)

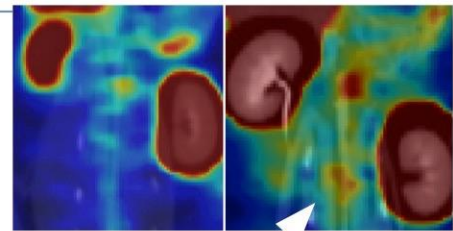


Aortic arch



PET imaging

CT (angio)



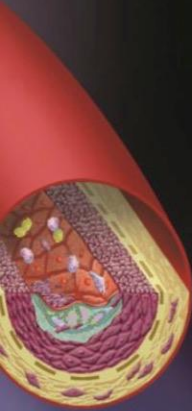
PET

CT (angio)

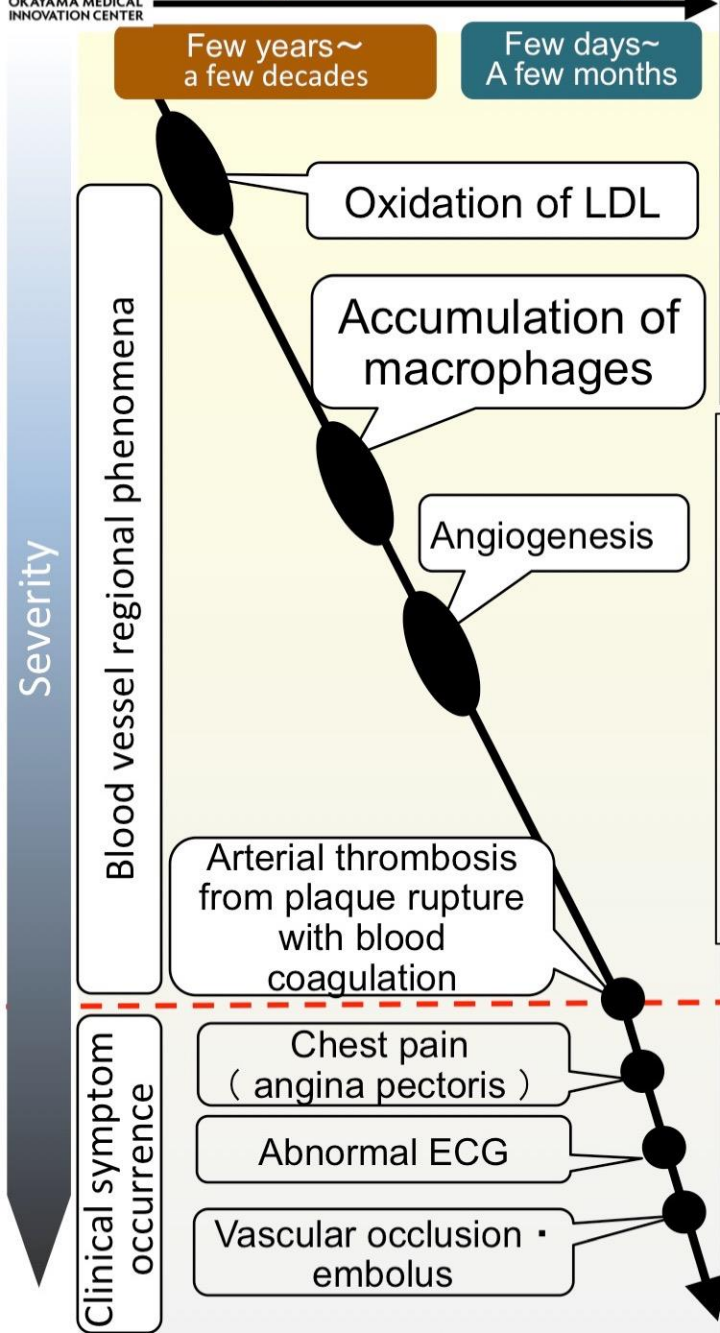
Abdominal Aorta  
(Branch to renal artery)

Control

WHHL



# Targeted therapy and diagnosis of atherosclerotic disease



Few years~ a few decades

Few days~ A few months

**Primary screening**

*in vitro* test kit AtherOx<sup>®</sup>  
( measurement of oxLDL/  $\beta$ 2GPI complex )  
(Patented)

Blood test

Lipid analysis

Oxidized lipids analysis by mass spectrometry

Lipids analysis link with process of purification by HPLC or antibody affinity

**secondary screening (PET imaging)**

Visualization of Unstable plaque  
Human anti-b2GPI-scFv antibody (Developing)

Thrombogenesis

Visualization of thrombus

Intact DV

Calcification of arterial media

Antibody against oxidized lipids specific for calcification focus (Developing)

Visualization of angiogenesis

Thinning of fibrous cap

angiogenesis

DI

nicked-DV

**Theranostics (combined therapy and diagnostic)**

Feedback of therapeutic effect

definitive diagnosis

CT imaging

catheterization

Angiogenesis inhibitor (siRNA)

DDS carrier composed of novel bio-degradable polymer

Targeted carrier with photosensitive nanocarrier

siRNA

RI

Amphiphilic polymer

Domain I





**Cardiovascular  
Solutions & Innovations, LLC**

# Bench-to-Bedside...

## Consulting Services



*In-Vitro*  
Diagnostics

### ABOUT US

Cardiovascular Solutions and Innovations, LLC (CSI) is Okayama University's first bio-venture locates outside Japan. With offices in South Bend, Indiana (USA), CSI offers consulting services to global research community. CSI helps usher translational research (TR) in cardiovascular medicine from the bench to the bedside.

### Clinical and Translational Research Platform

CSI assists laboratory scientists, researchers, and clinicians to coordinate their efforts toward a common goal. As a bio-venture of Okayama University, CSI's access to state of the art facilities and equipment provides the platforms necessary to facilitate the innovation and advancement of medical devices.



IgG  
(150 kDa)



scFv  
(25 kDa)

Antibody  
Humanization

### MISSION

Building on years of experience in the development and commercialization of medical devices, CSI works diligently to assist its partner in achieving their project goal in an expeditious manner.

### Medical Device Licensing

With a proven track record in medical device registrations, CSI assists its partners to prepare, submit, and secure regulatory clearance for their medical devices.



*In-Vivo*  
PET Imaging



Contact



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