

# **Gut Microflora Influences Pathology in the Kawasaki Disease (KD) Vasculitis Mouse Model**

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# Presenter Disclosure Information

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Vasculitis Mouse Model**

**FINANCIAL DISCLOSURE:**

No relevant financial relationship exists

# Intestinal Microbiota and Disease

**Health**

**Disease**

**Immune system**

**Metabolism**



**IBD**

**(inflammatory Bowel disease)**

**allergy**

**Arteriosclerosis**

# Changes in intestine of KD patients

*Pediatric Research* (1996) **39**, 622–624; doi:10.1203/00006450-199604000-00010

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PEDIATRIC RESEARCH

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## Immunohistochemical Studies on Small Intestinal Mucosa in Kawasaki Disease

SATORU NAGATA, YUICHIRO YAMASHIRO, MASATO MAEDA, YOSHIKAZU OHTSUKA, AND  
KEIJIRO YABUTA

*Department of Paediatrics, Juntendo University School of Medicine, Tokyo, Japan*

*Acta Pædiatr* 91: 783–788, 2002



**Macrophage/dendritic cells and activated CD4<sup>+</sup> T cells were significantly increased in the lamina propria of KD patients in the acute phase.**

Characteristic profile of intestinal microflora in Kawasaki disease

S Takeshita, I Kobayashi<sup>1</sup>, Y Kawamura, T Tokutomi and I Sekine

*Department of Pediatrics, National Defense Medical College, Tokorozawa, Saitama, Japan; Chemotherapy Division<sup>1</sup>, Mitsubishi-Kagaku Bio-Clinical Laboratories, Tokyo, Japan*

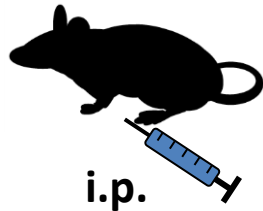
**KD patients had a significantly lower incidence of Lactobacillus than disease control patients**

# Kawasaki Disease Vasculitis Mouse Model

Arthritis Rheum, 1985 Jun;28(6):652-9,

Coronary arteritis in mice following the systemic injection of group B *Lactobacillus casei* cell walls in aqueous suspension.

Lehman TJ, Walker SM, Mahnovski V, McCurdy D.



Coronary  
Arteritis

70-80% C57BL/6

*Lactobacillus casei* cell wall extract (LCWE)

Day 3

Mononuclear  
cells in  
adventitia

Day 14

Focal, asymmetric  
invasion of arterial  
wall, Lymphocytic

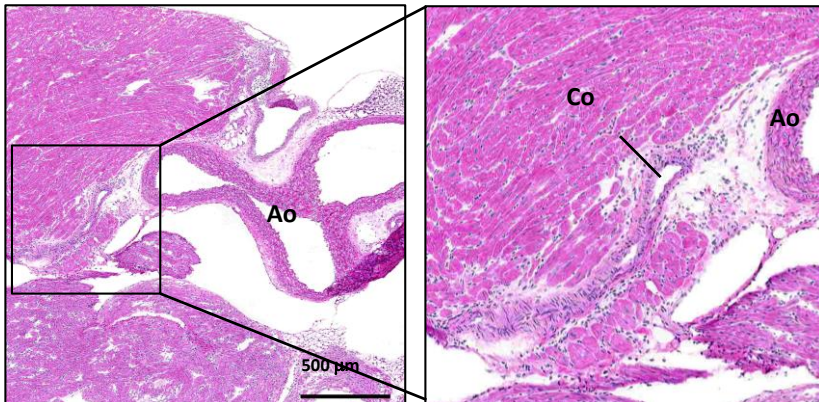
Day 28

Circumferential  
lesion with marked  
proliferation of  
intima/media

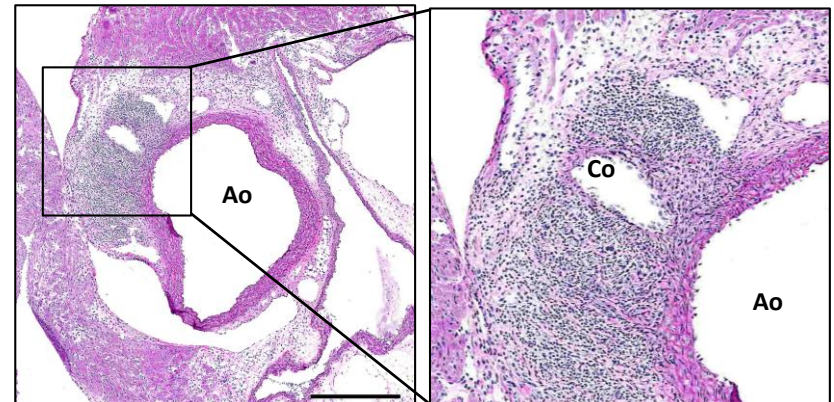
Day 56

Fibrous tissue,  
marked  
narrowing

Control



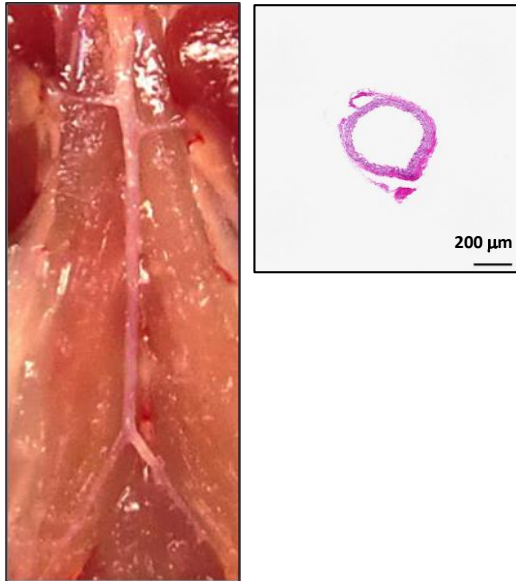
LCWE



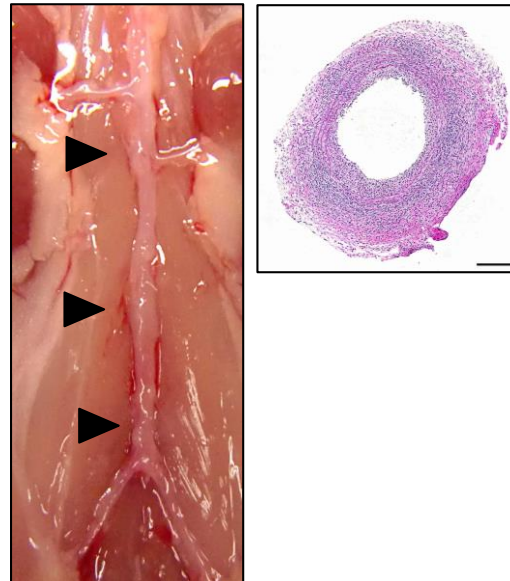
# LCWE-induced KD mouse model develops abdominal aorta aneurysms

## Abdominal Aorta

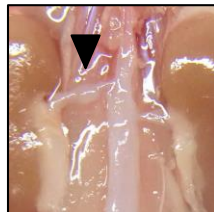
Control



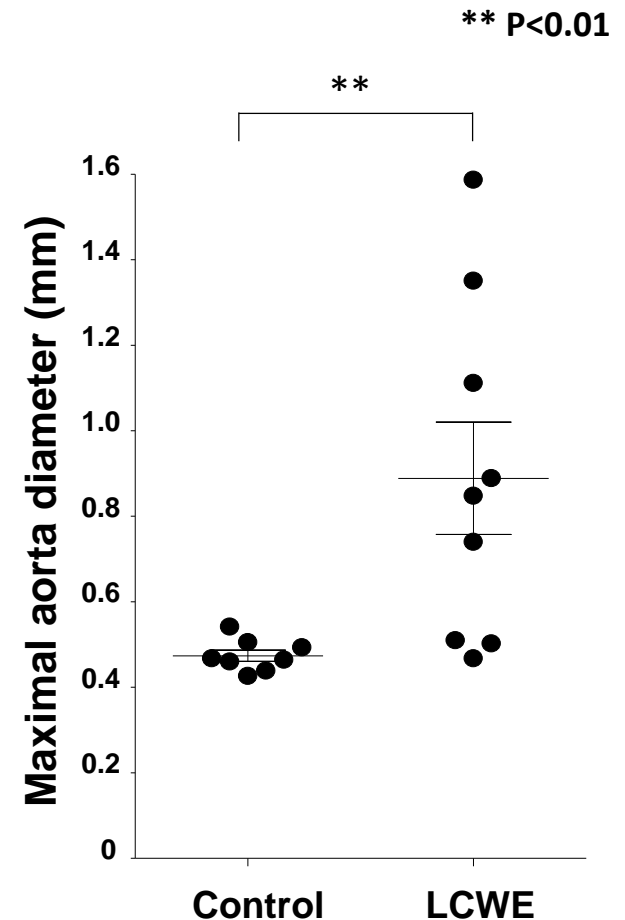
LCWE



Renal artery

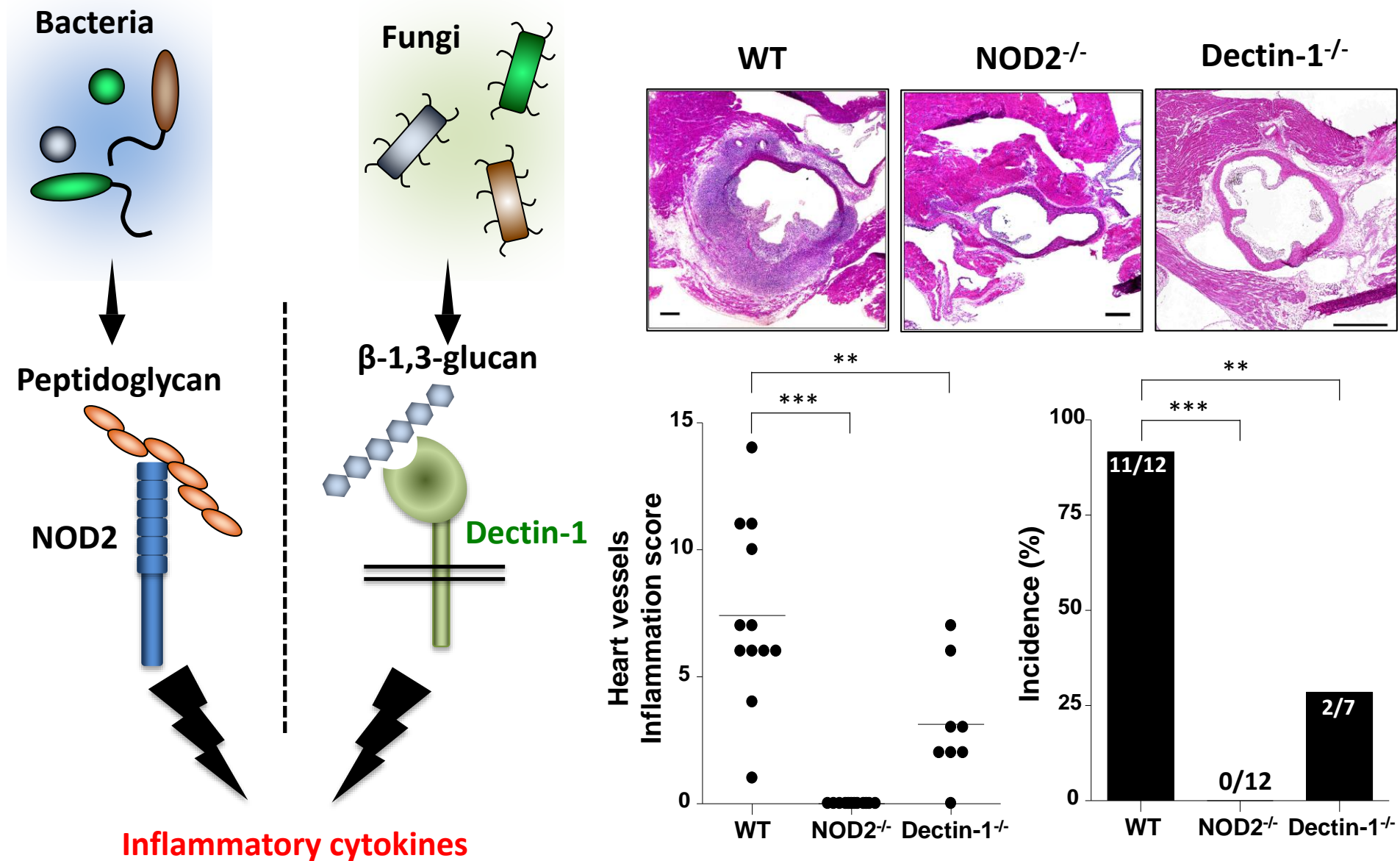


Iliac artery



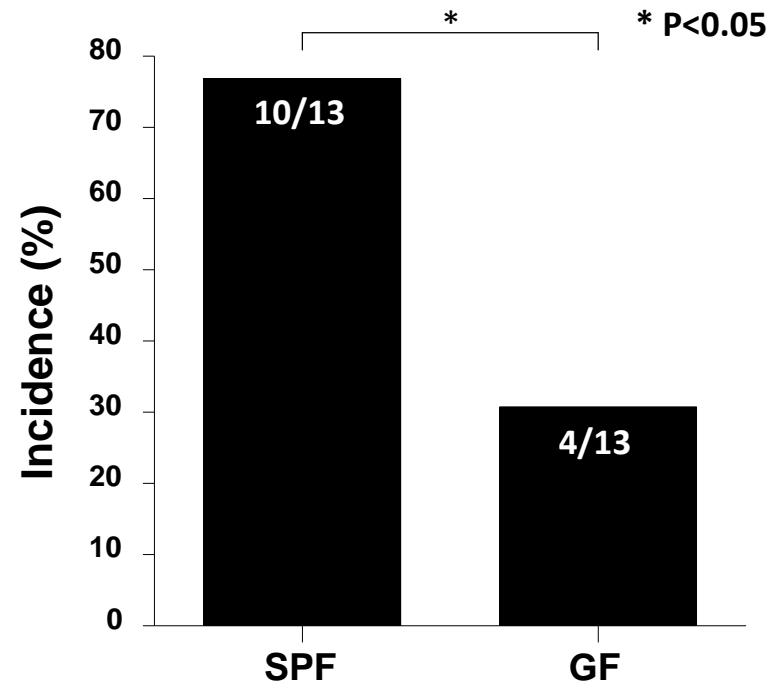
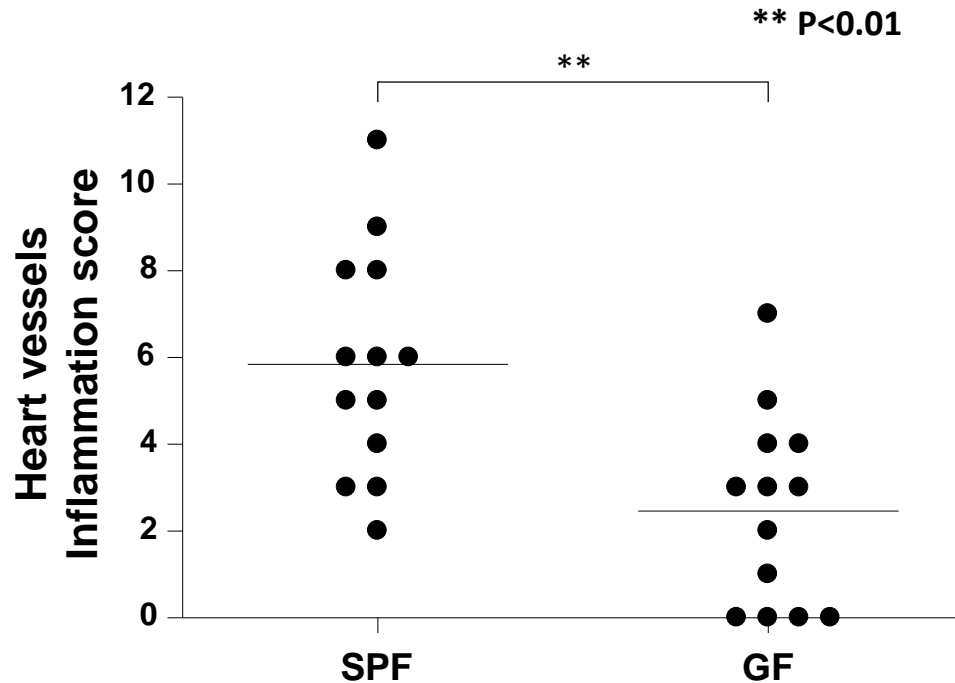
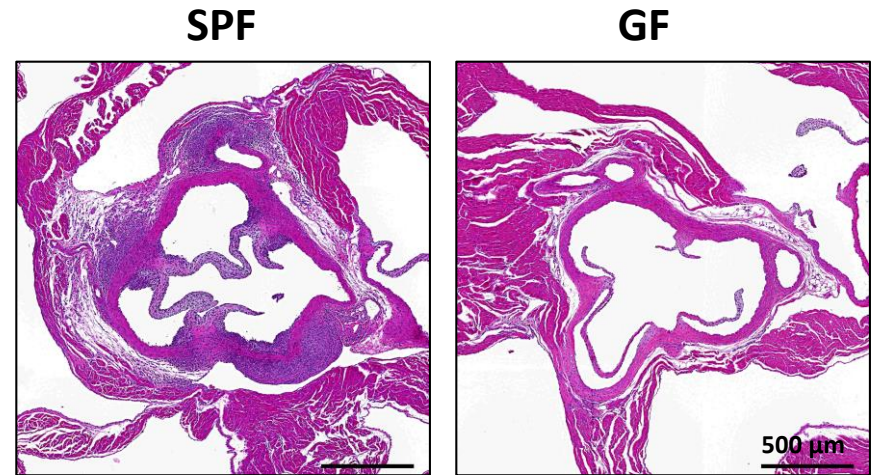
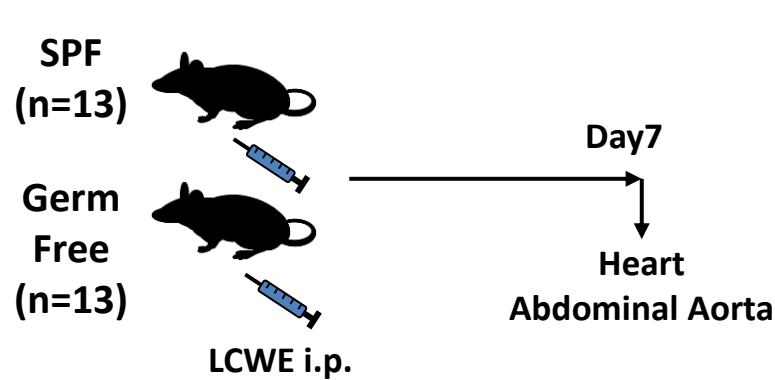


# NOD2<sup>-/-</sup> and Dectin-1<sup>-/-</sup> mice are protected from LCWE-induced KD vasculitis



\*\* P<0.01, \*\*\*P<0.001

# Germ-Free mice develop markedly decreased cardiovascular lesions in KD mouse model (Coronary lesions)



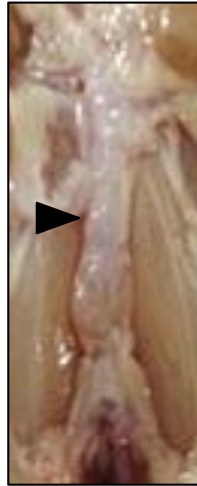


# Germ-Free mice develop markedly decreased cardiovascular lesions in KD mouse model (abdominal aorta lesions)

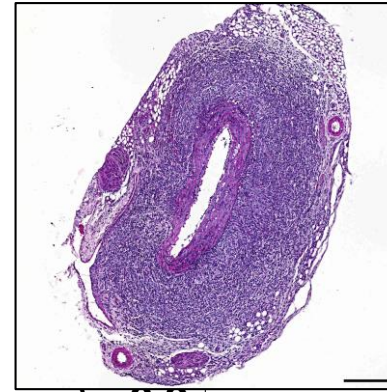
Naïve



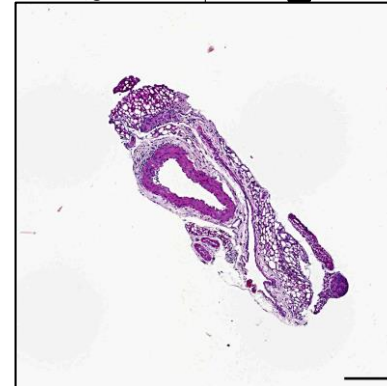
KD SPF



KD GF



aorta diar  
0.9  
0.6

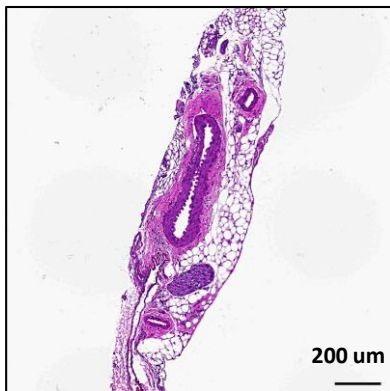


\*\*\*  $P < 0.001$

\*\*\*

SPF

GF



# Depletion of commensal fungi and bacteria with fluconazole and antibiotic treatment



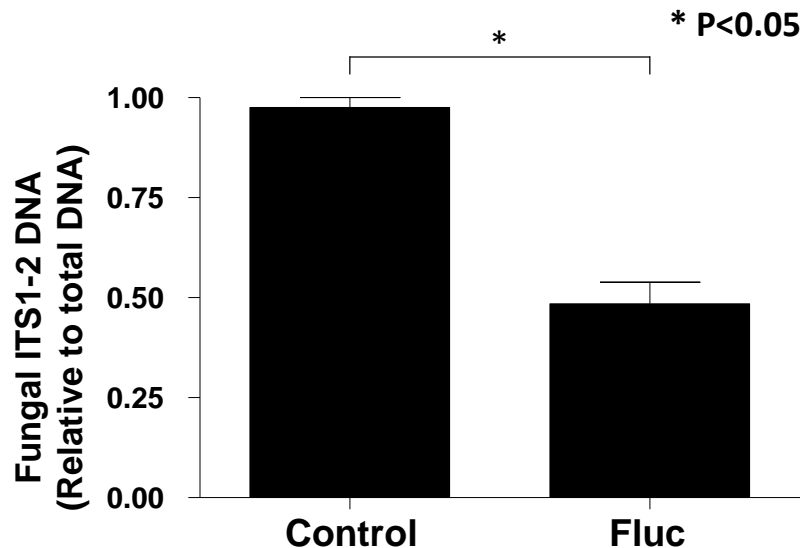
**Anti-fungal drug (Fluconazole; Fluc)**

**and/or**

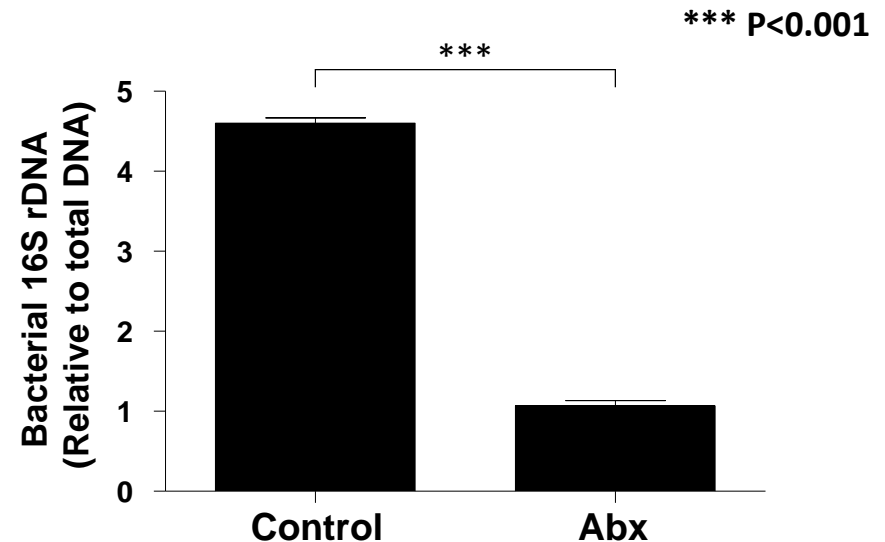
**Antibiotics cocktail (Abx)**

**(Neomycin, Ampicillin, Vancomycin, Metronidazole)**

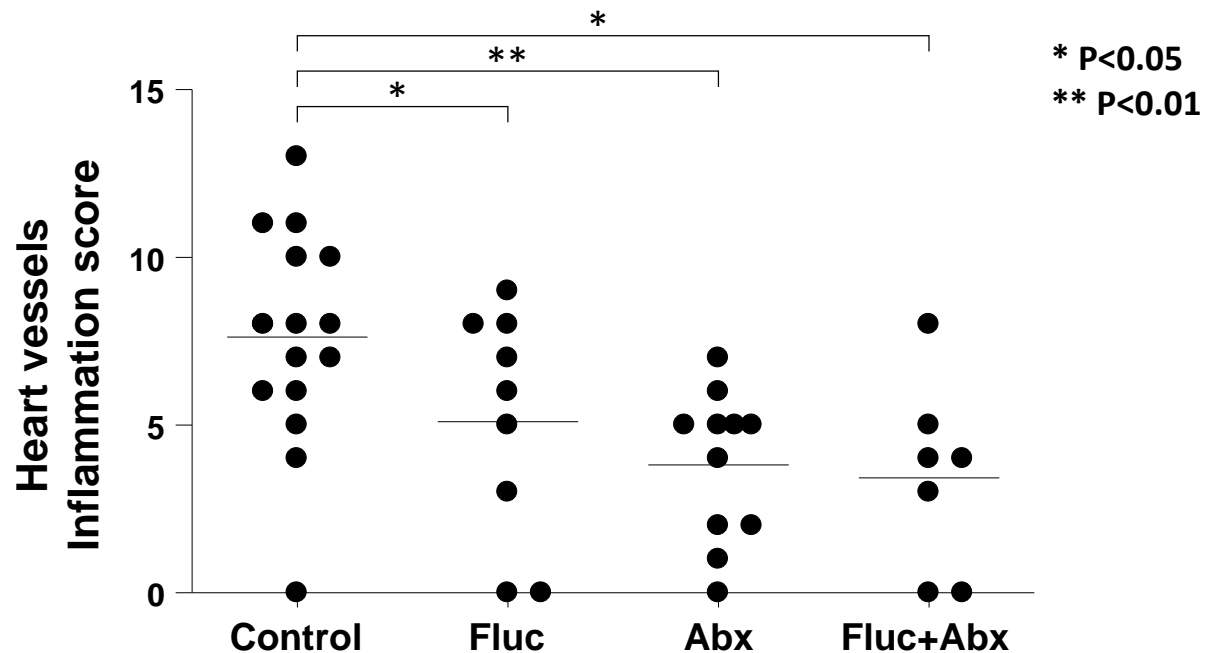
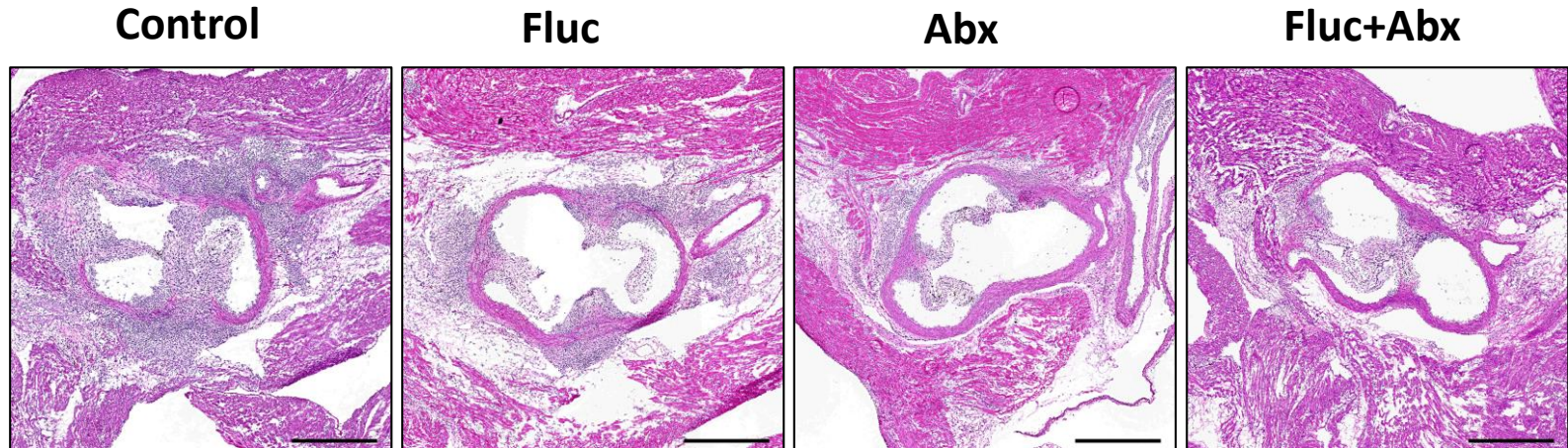
## Fungi amount



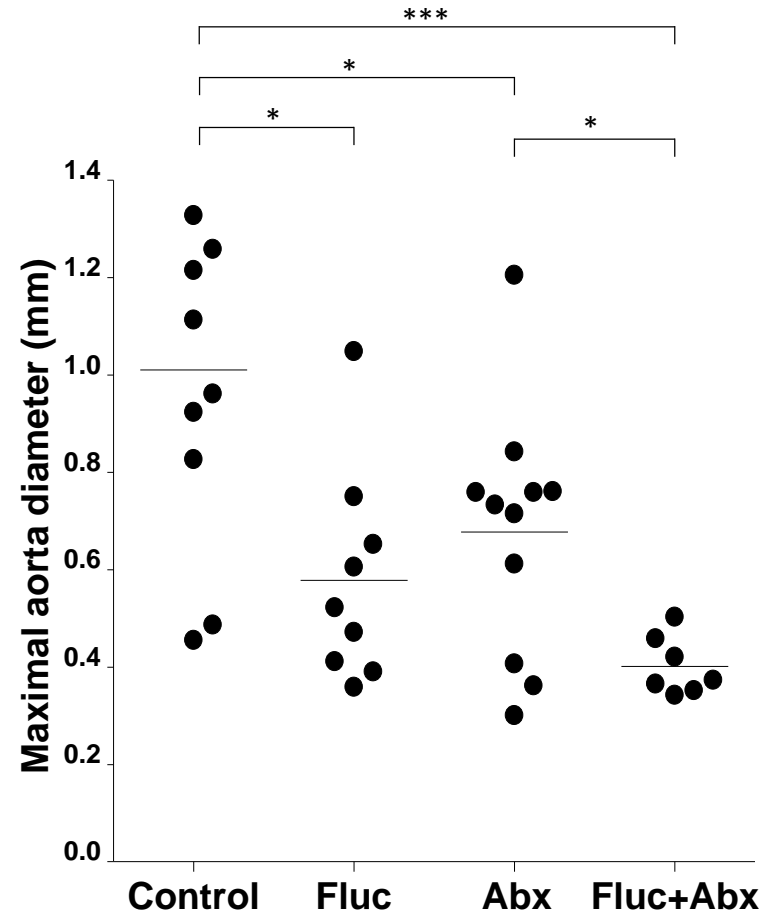
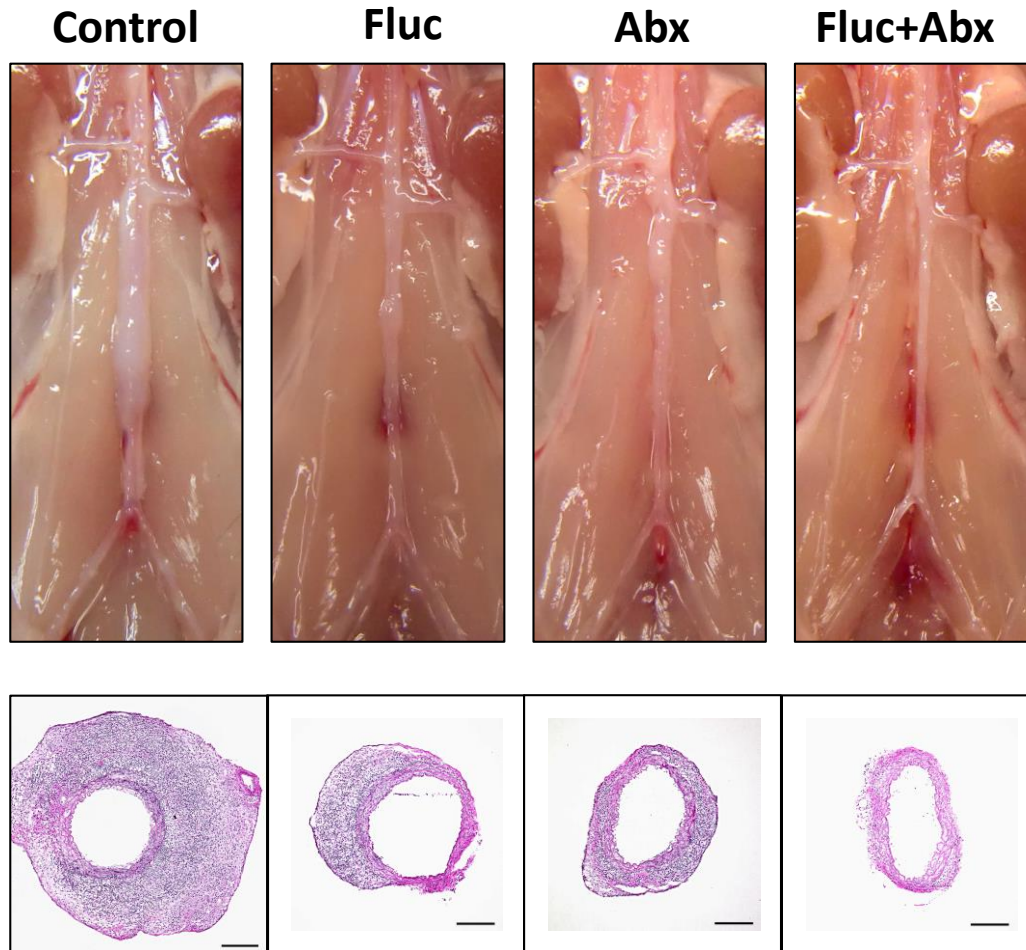
## Bacteria amount



# Fluconazole and/or antibiotics treatment decreased cardiovascular lesions in KD mouse model



# Fluconazole and/or antibiotics treatment decreased cardiovascular lesions in KD mouse model



\*  $P < 0.05$ , \*\*\*  $P < 0.001$

# Intestinal permeability and disease development

Gut Microflora

Host

Bacteria

Fungi

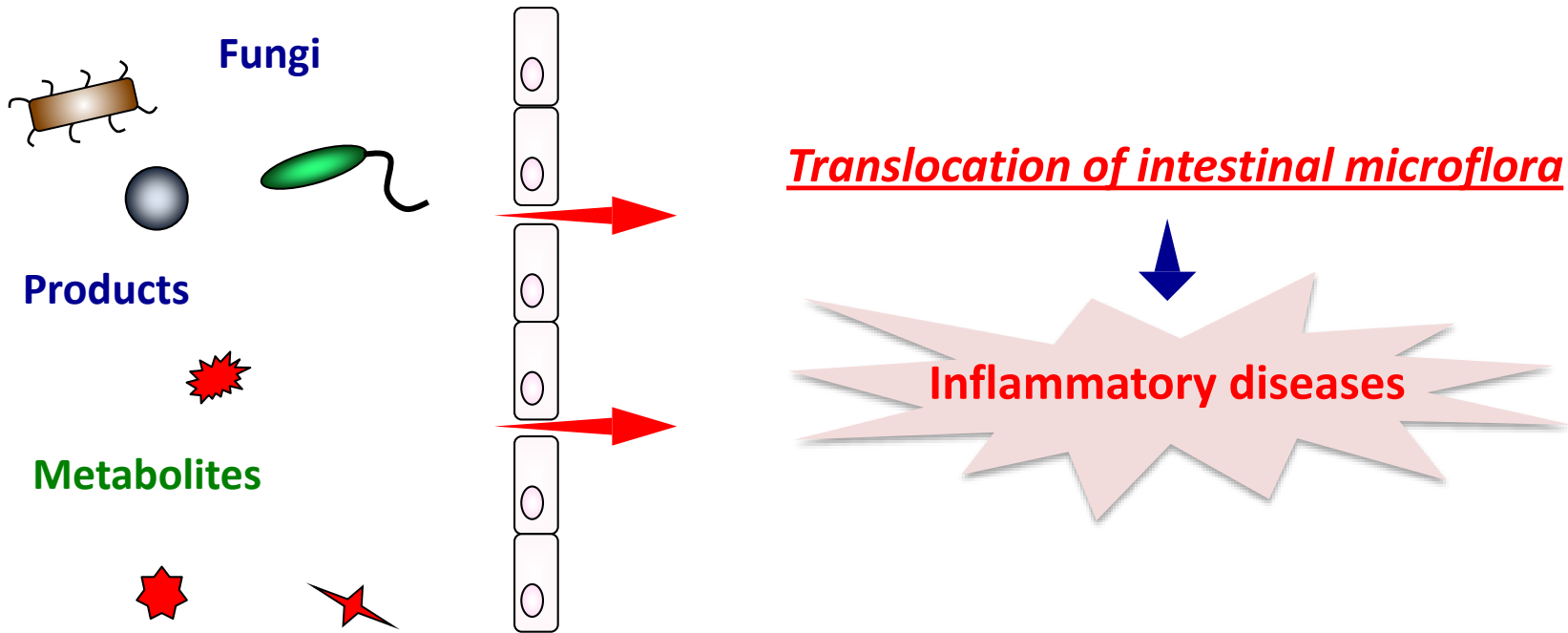
Products

Metabolites

Intestinal barrier dysfunction

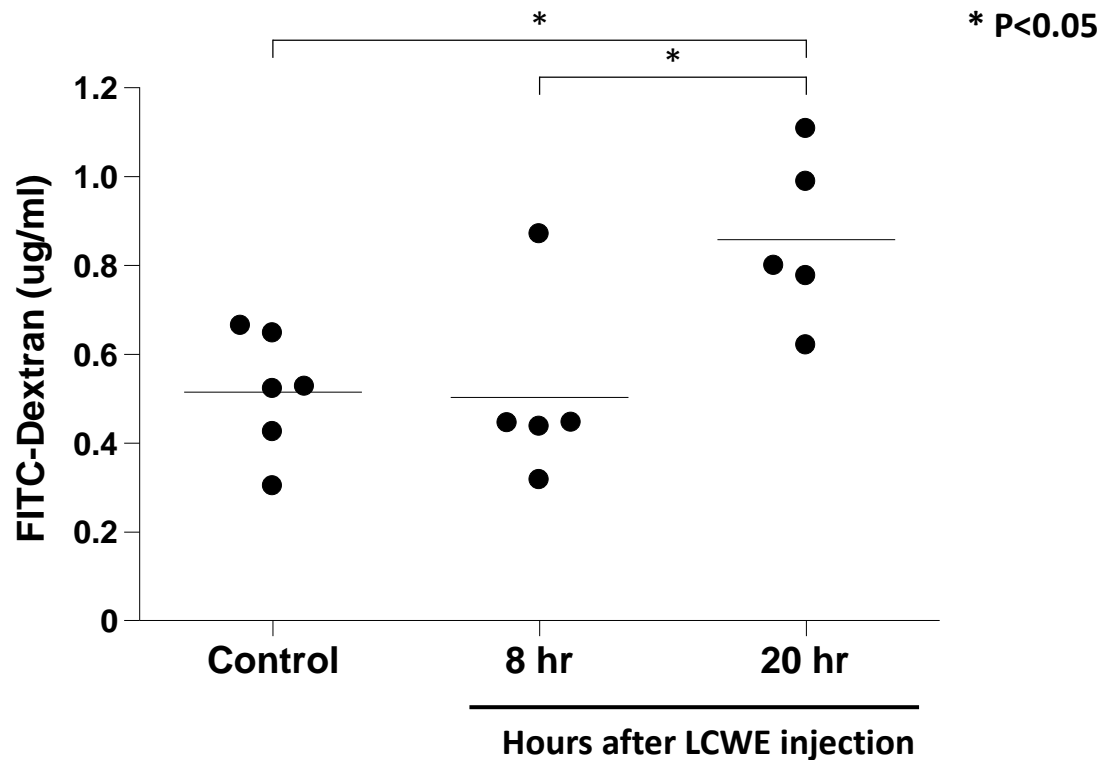
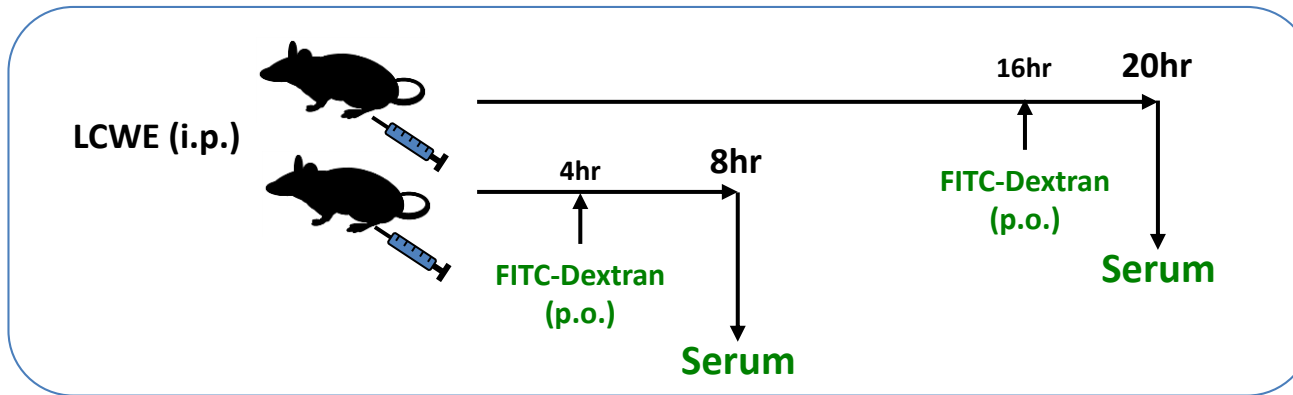
Translocation of intestinal microflora

Inflammatory diseases





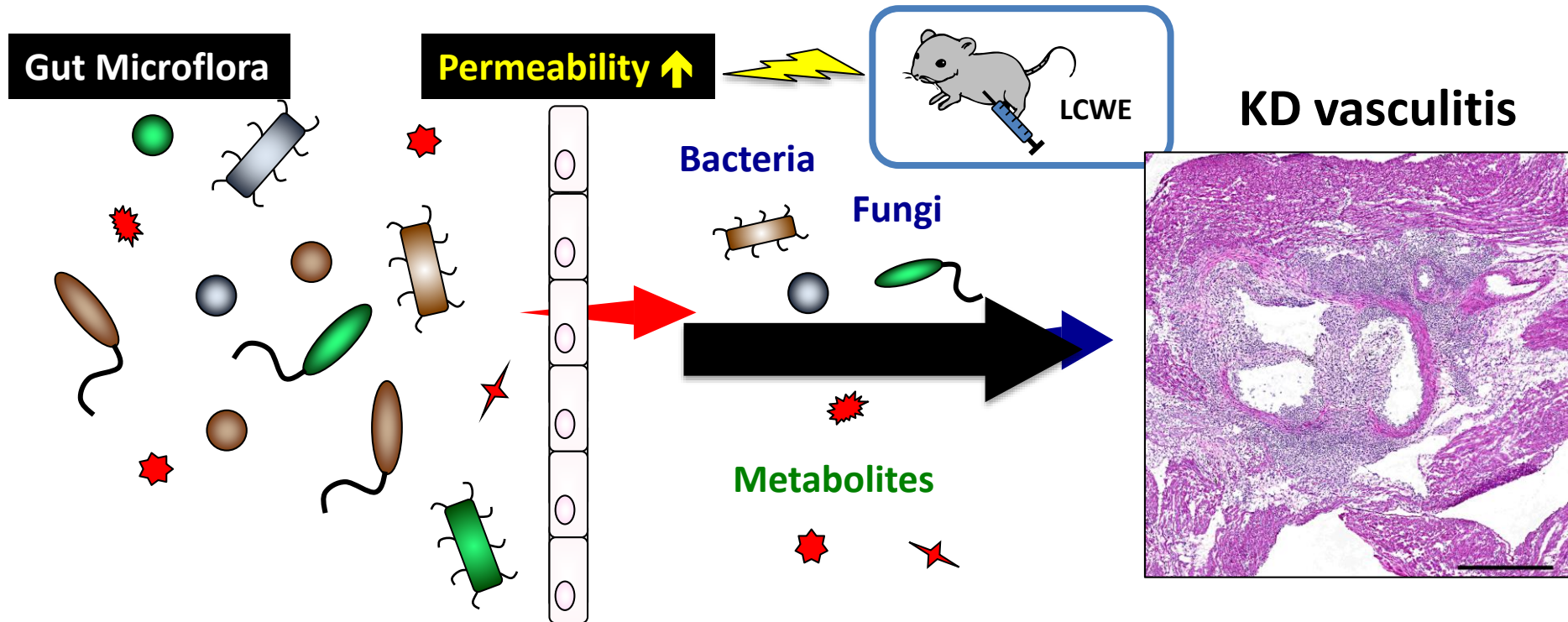
# LCWE injection increases intestinal permeability





# Conclusions

- ✓ LCWE-induced cardiovascularitis was decreased in germ free mice
- ✓ Depletion of gut commensal fungi and bacteria diminished KD vasculitis
- ✓ LCWE injection increased intestinal permeability
- ? Role of microbiome in KD pathogenesis, new diagnostic/therapeutic strategies



# Acknowledgement

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