Pharmacogenomics and Therapeutic Target Validation of Cardiovascular Disease Models

Toshio Tanaka MD, PhD

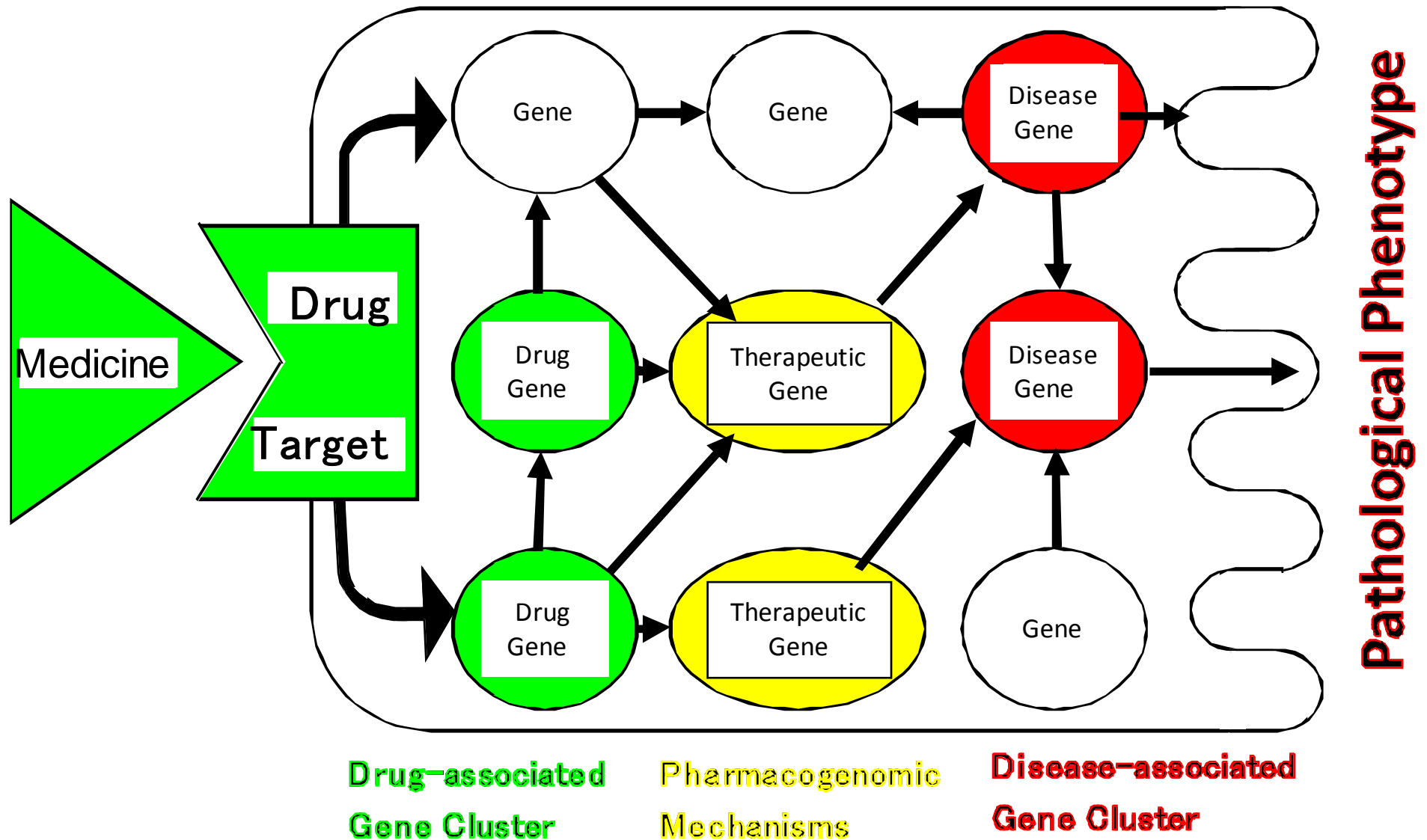Department of Molecular and Cellular Pharmacology

Pharmacogenomics and Pharmacoinformatics

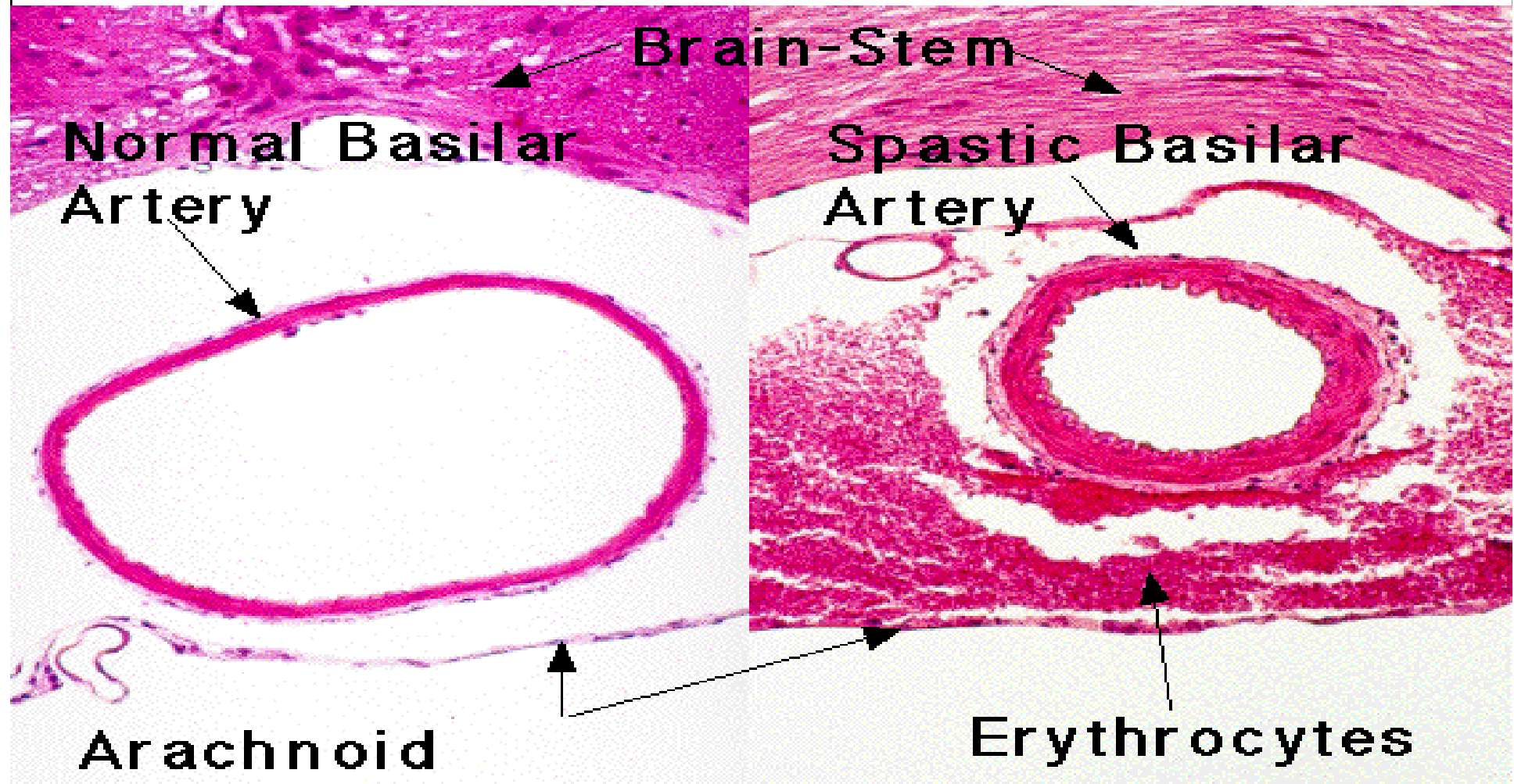Mie University Graduate School of Medicine

February 25, 2009

UNAM, Mexico City, Mexico

Pharmacogenomics Network Analysis of Therapeutic Genes
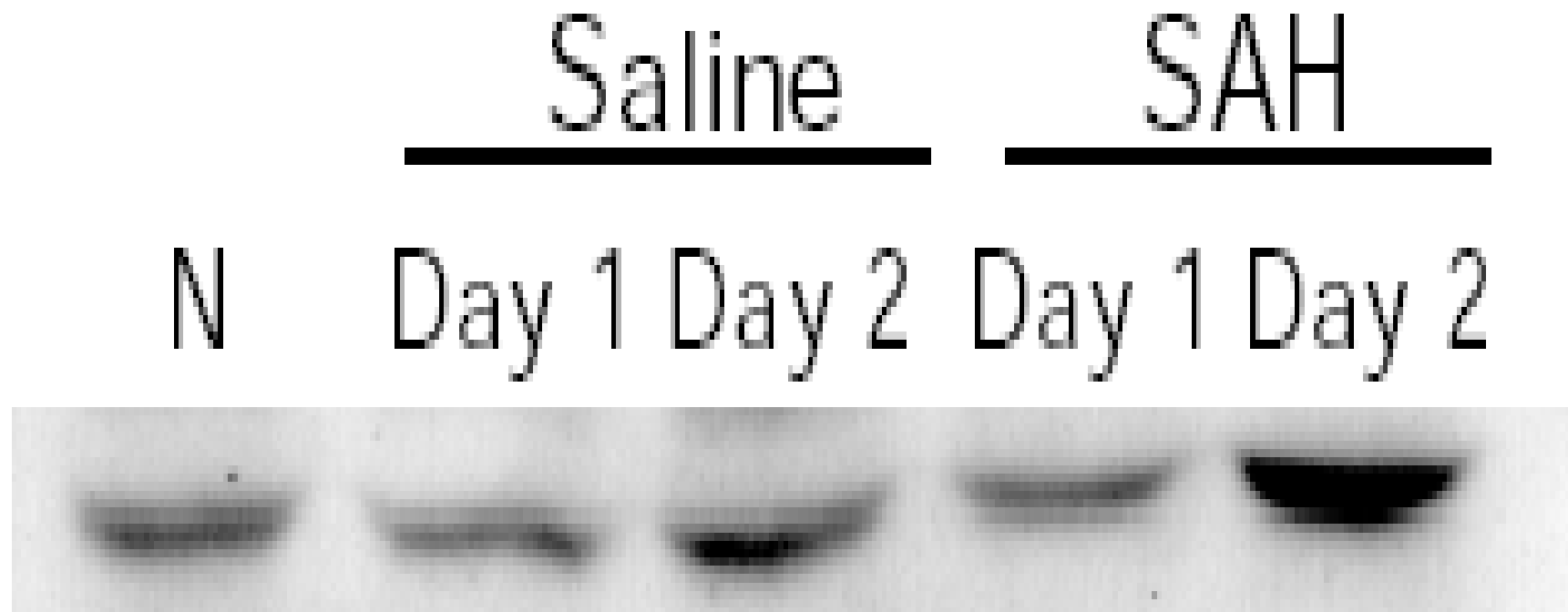

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Rat Cerebral Vasospasm Model

Brain-Stem

Normal Basilar Artery

Spastic Basilar Artery

Arachnoid

Erythrocytes

HE staining (x 100)

HSP72 Protein after SAH

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HSP72 Protein after SAH and Antisense

Saline   SAH   Antisense   Sense

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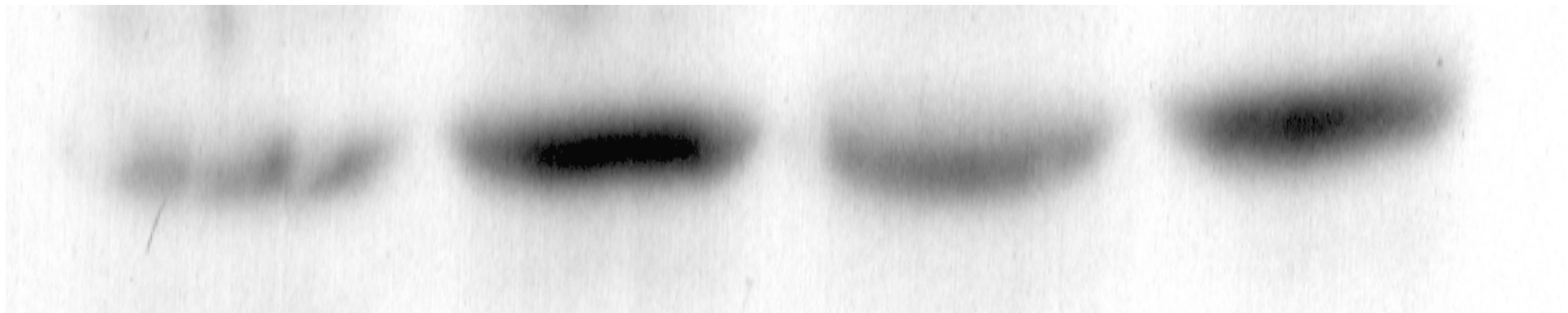
Effect of Antisense HSP72 ODN on Cerebral Vasospasm
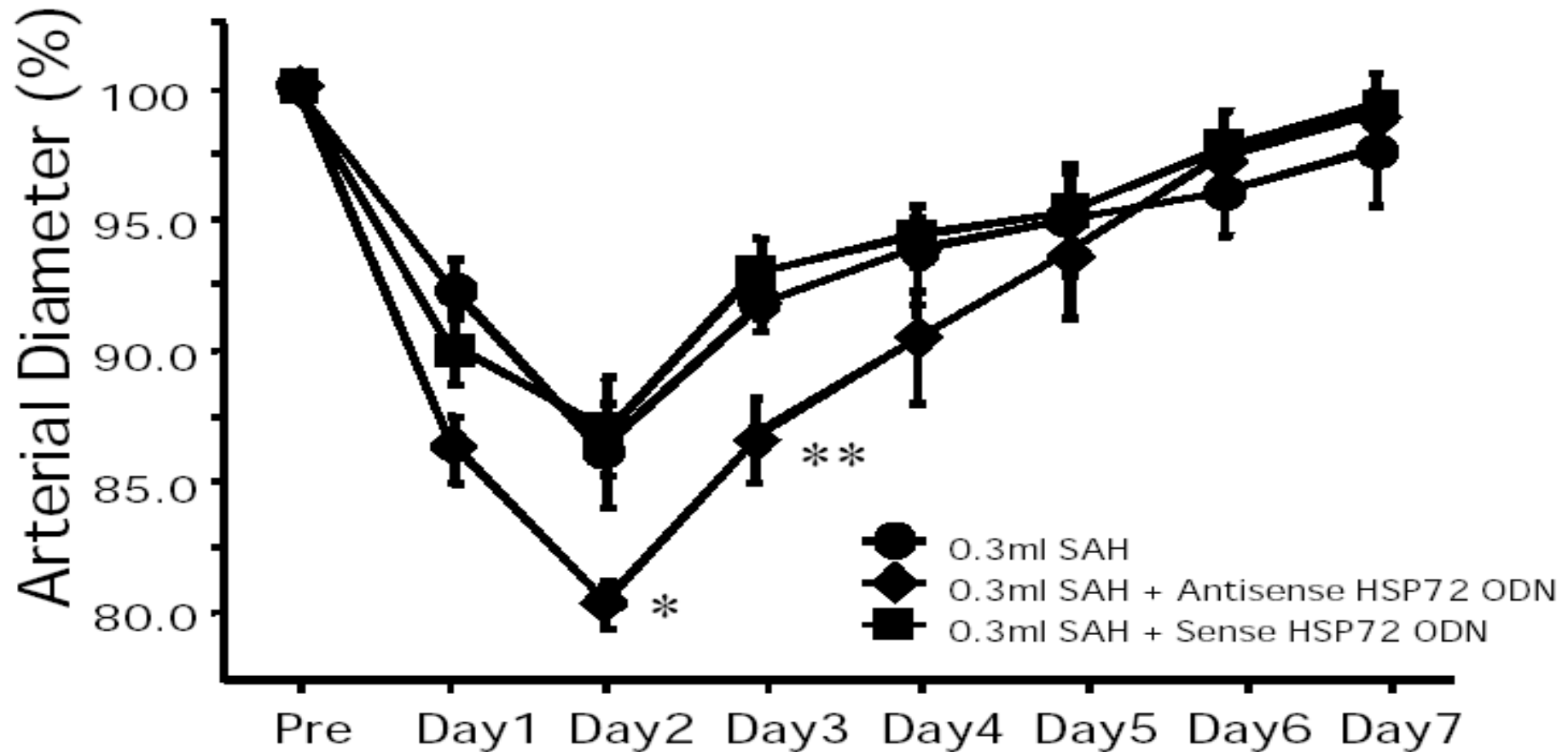
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Basilar artery (24 hours)

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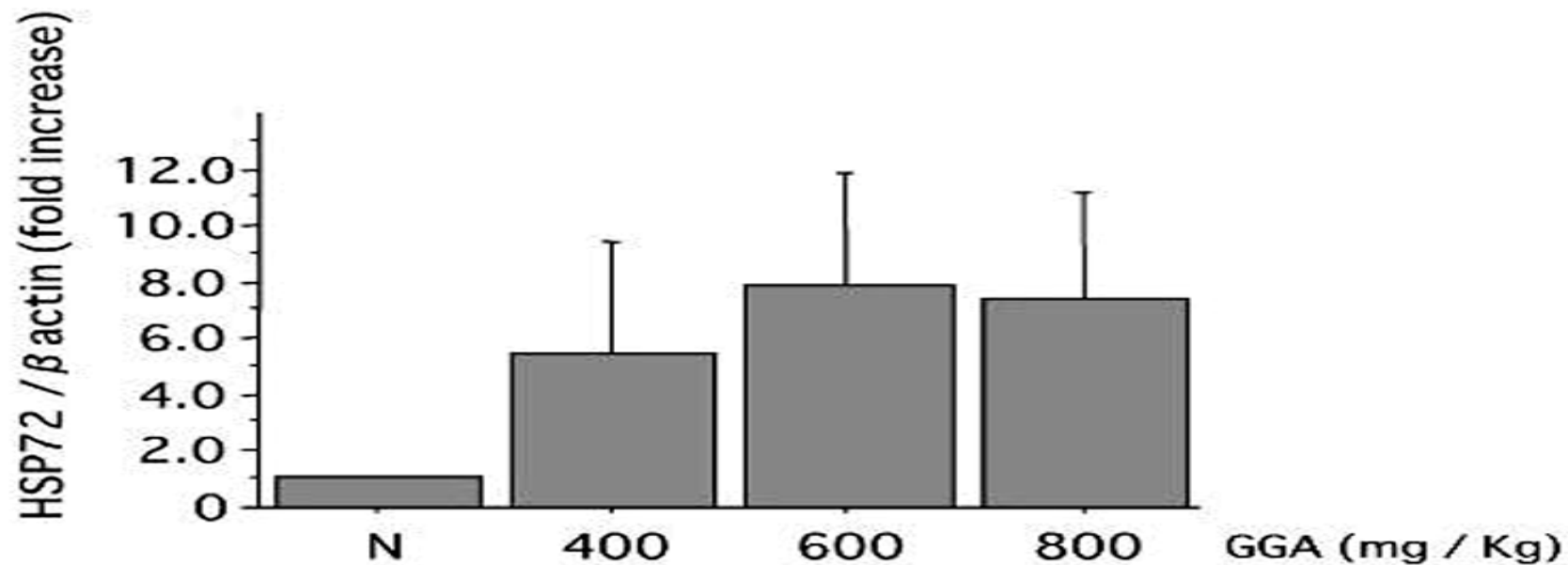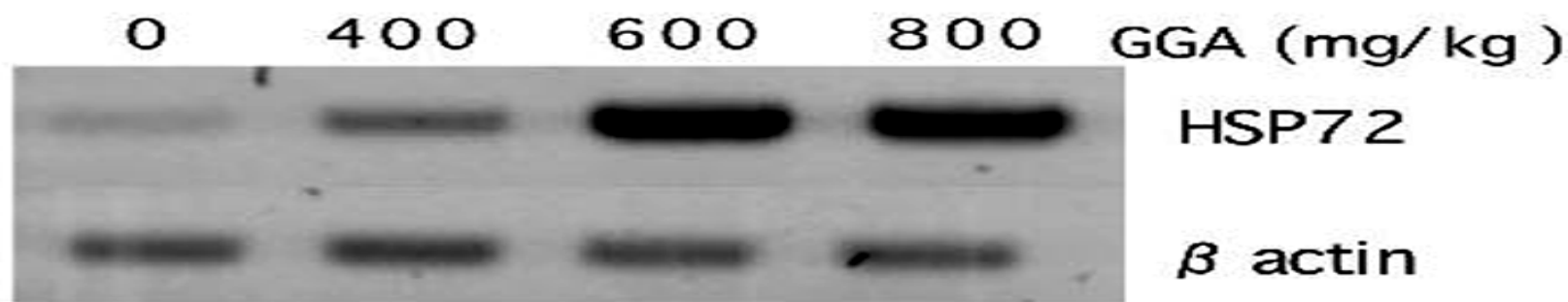
Effect of GGA on HSP72 Gene Expression
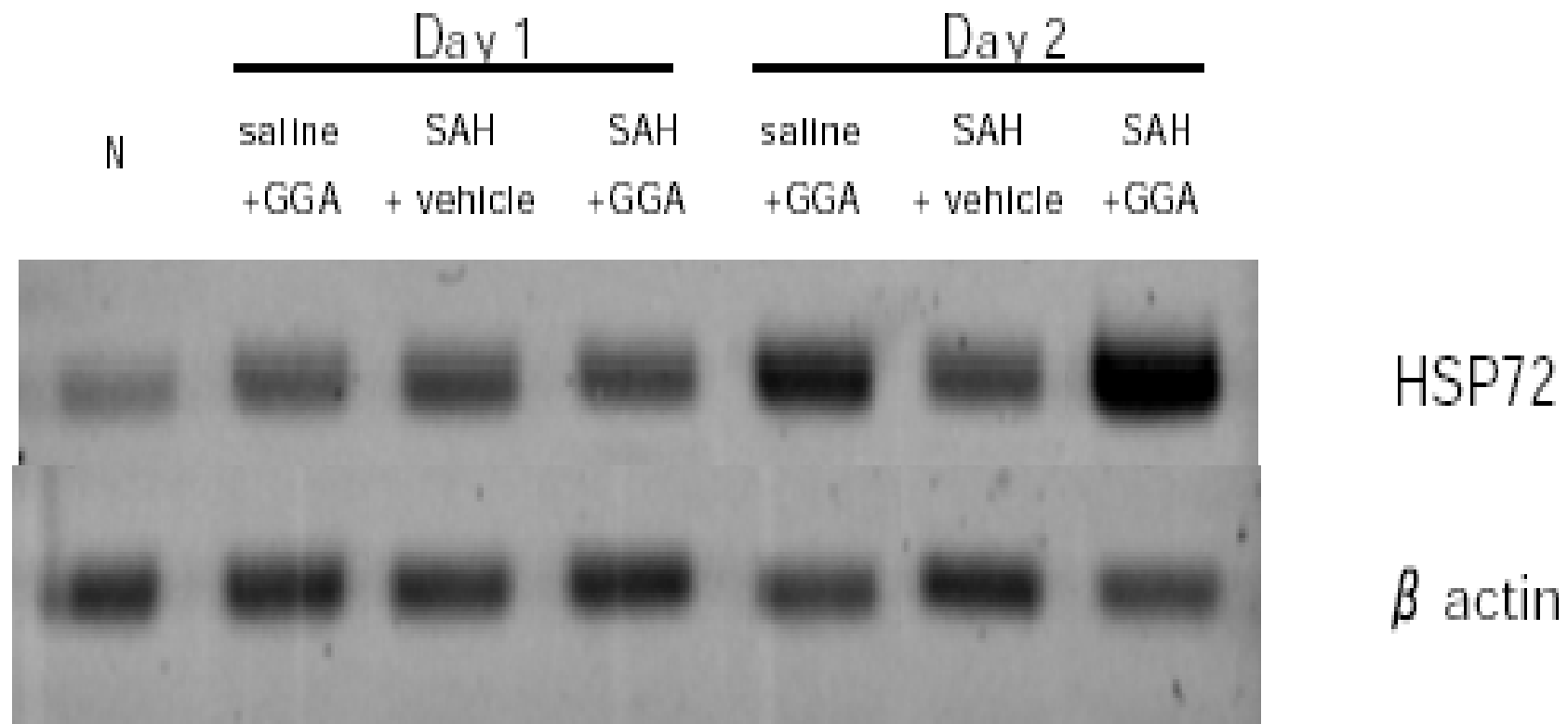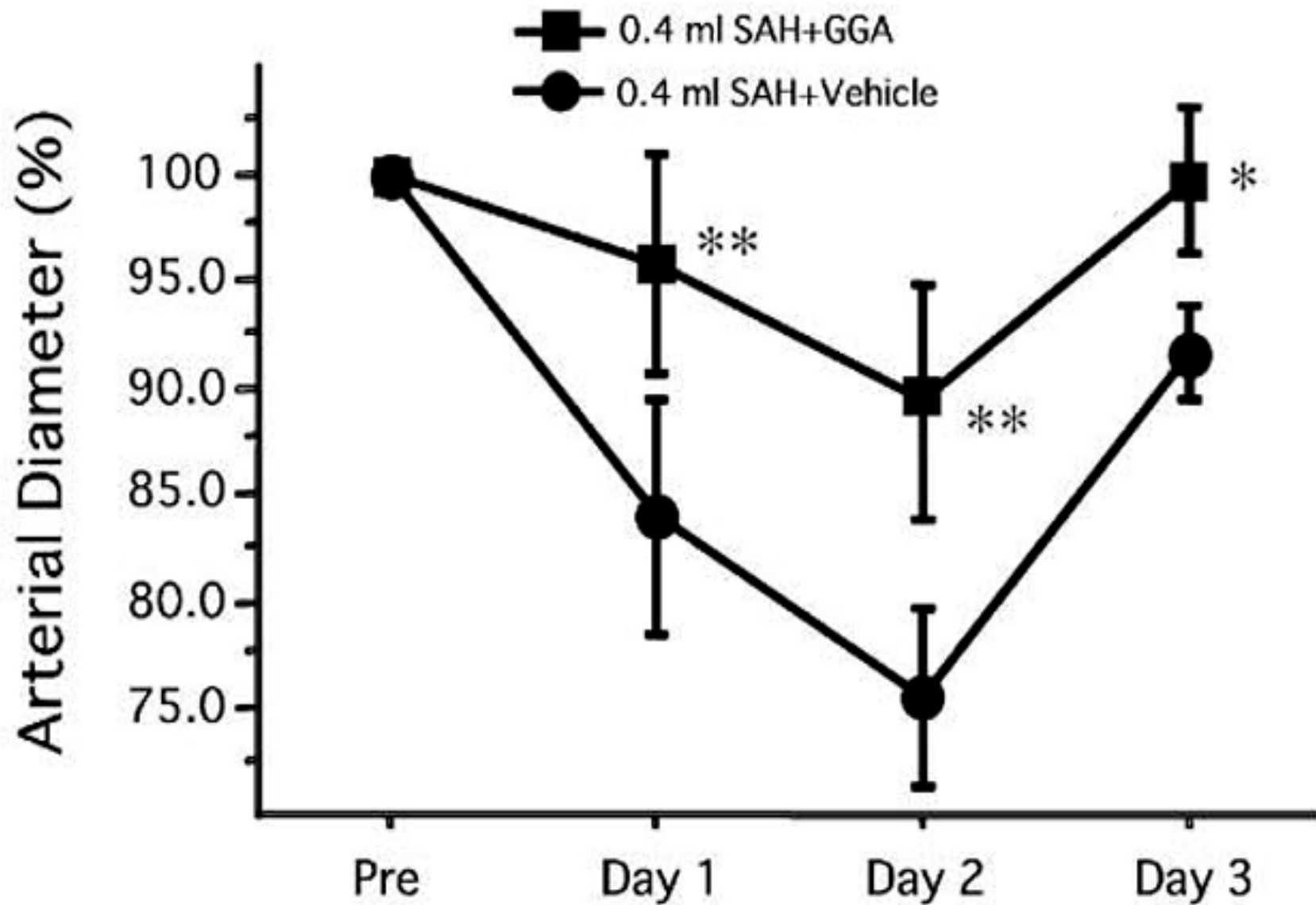
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Pharmacogenomics network analysis in treatment of cerebral vasospasm by GGA
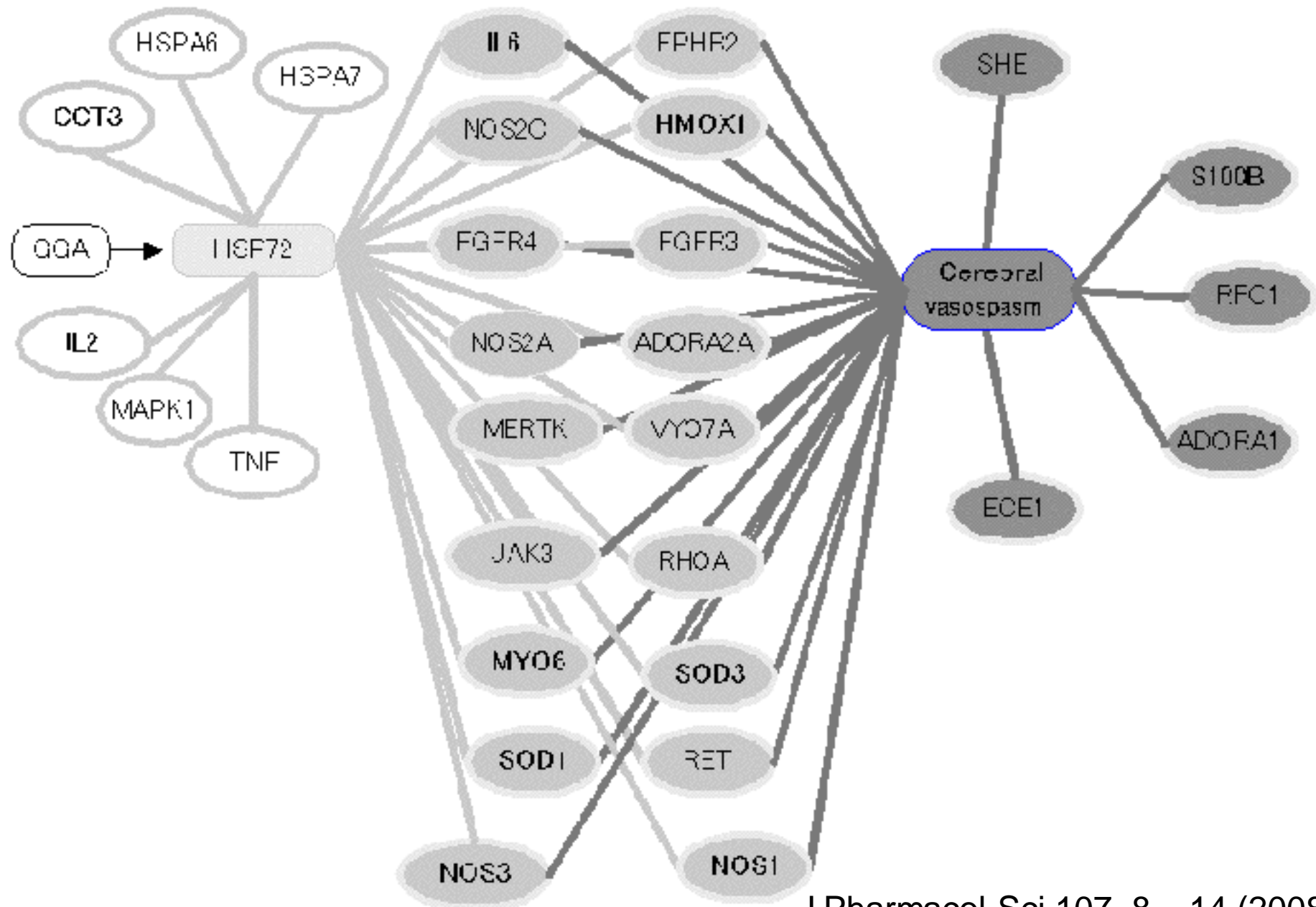
Heme Oxygenase – 1 mRNA in Rat Cerebral Vasospasm

Legend:
- pre-injection
- "1-saline" group
- "2-saline" group
- "1-hemorrhage" group
- "2-hemorrhage" group

Y-axis: HO-1/HO-2

X-axis groups: Basilar Artery, Brain-stem, Cerebellum, Occipital Lobe, Frontal Lobe, Parietal Lobe (each with 10 min, Day 1, Day 7, Day 12)
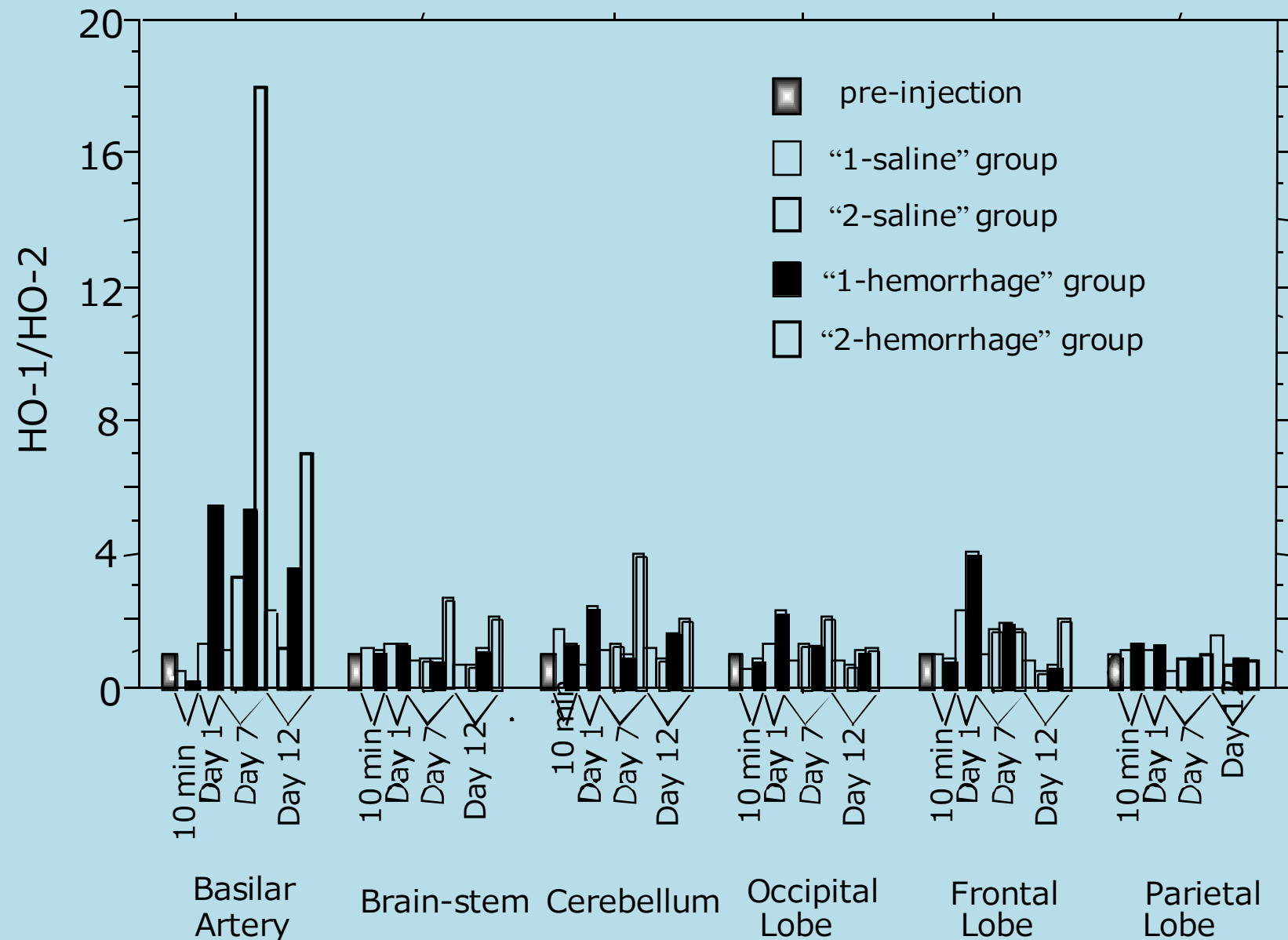
Effect of Antisense HO−1 ODN on Angiographic Vasospasm in Rat SAH Model

% Change in Vessel Diameter

■ sense HO-1 ODN

▲ scrasmbled ODN

● antisense HO-1 ODN

J.Clin. Invest. 104:59-66(1999)
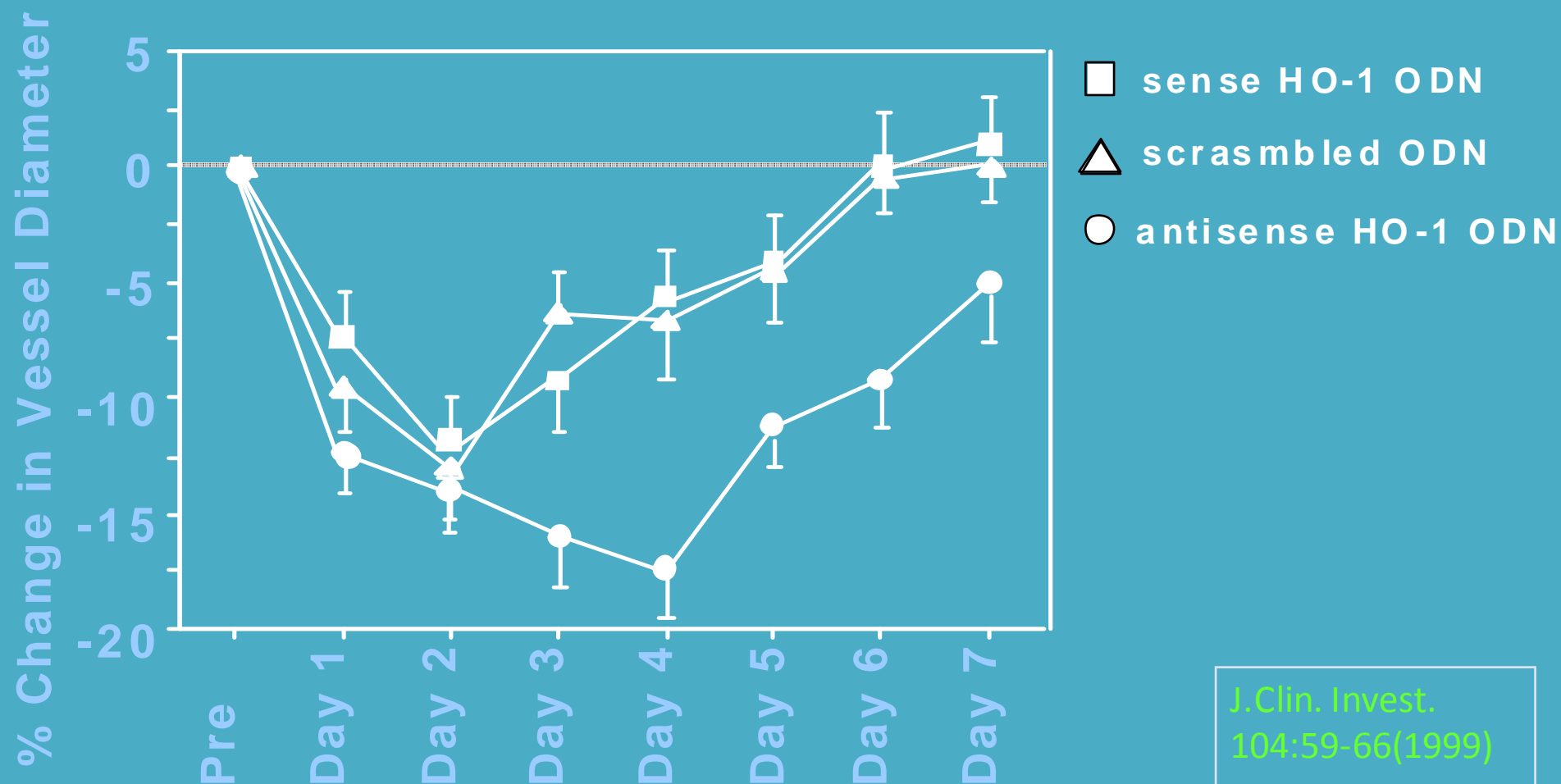
Pharmacogenomics network analysis in treatment of cerebral vasospasm by AVS(nicaraven)

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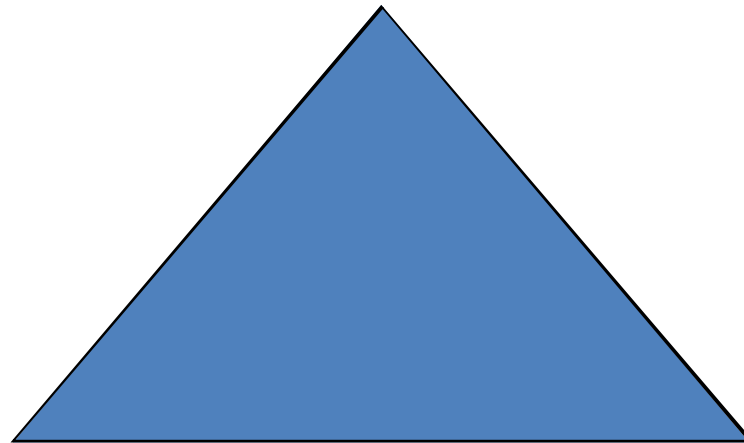Department of Molecular and Cellular Pharmacology, Pharmacogenomics and Pharmacoinformatics、Mie University Graduate School of Medicine
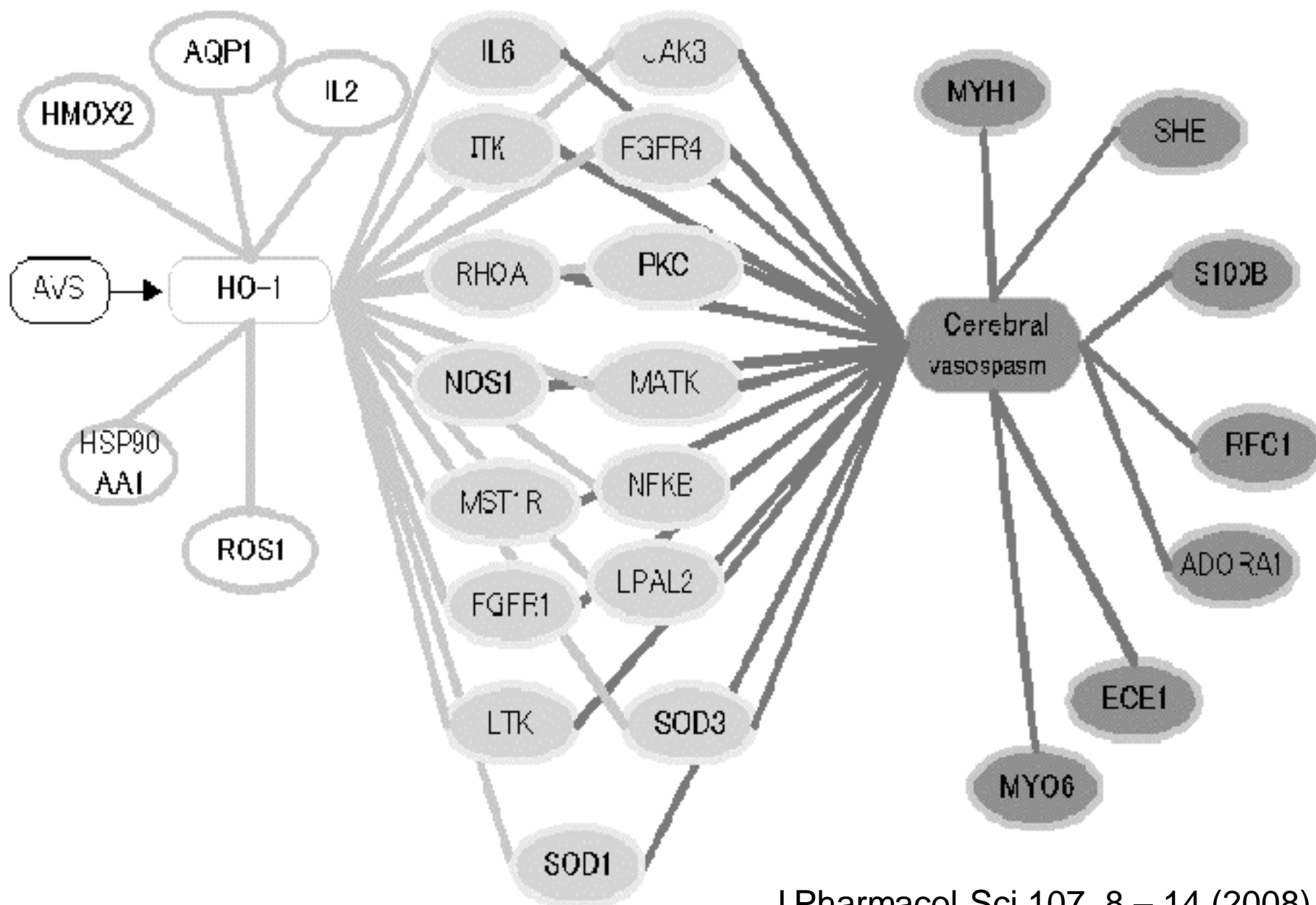
Comparative Genomics of Disease Models

Human（2003）

Rat/Mouse
（2005/2002）
Low Throughput
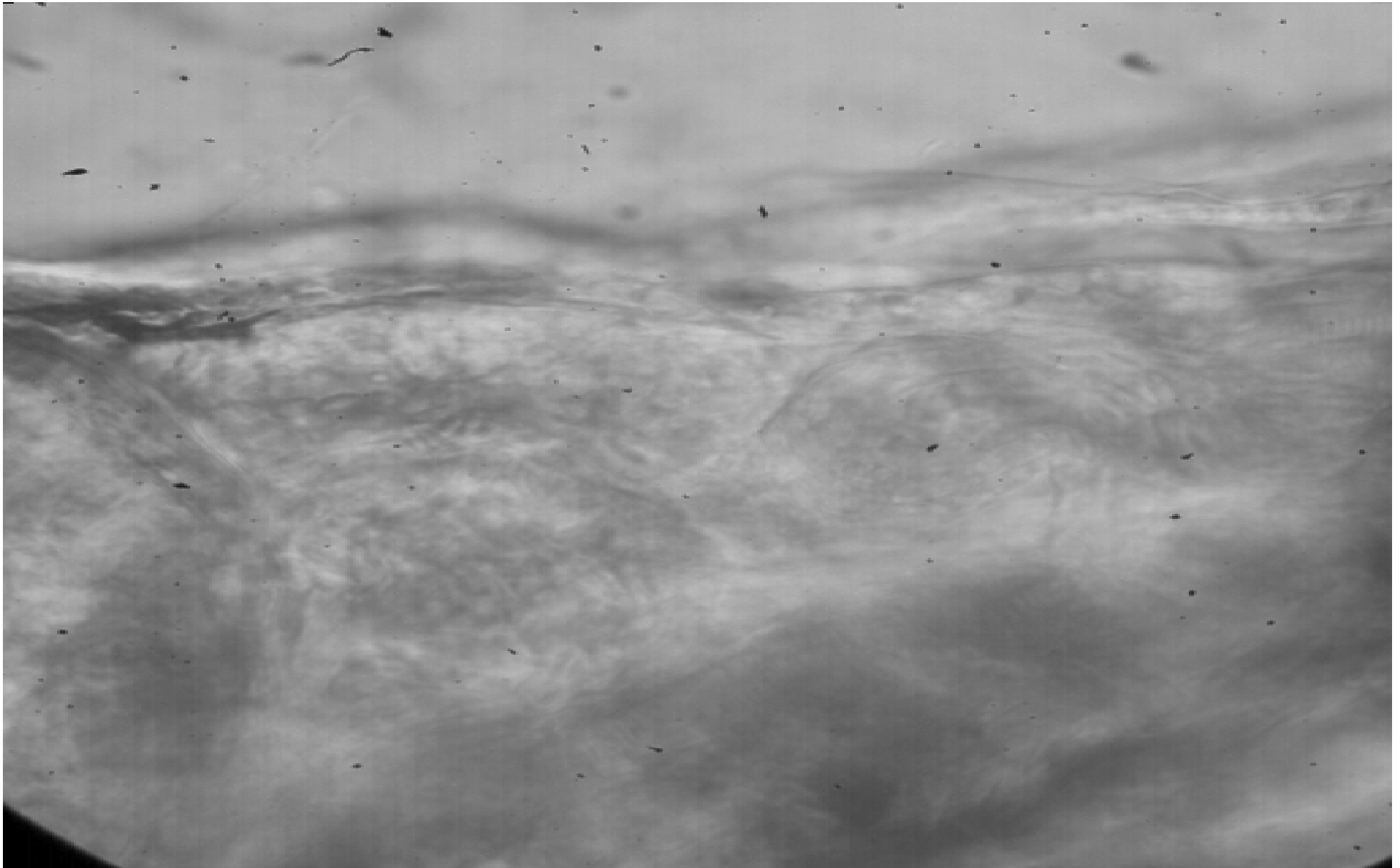
Zebrafish
（2009）
High Throughput

Advantages of Zebrafish as Disease Model Animal

- 1. Short reproductive cycle.
- 2. Large number of offspring per mating.
- 3. Embryos are transparent allowing internal organs and neurons to be visualised.
- 4. Strong correlation between human genetics, anatomy and disease.
- 5. Rapid layout of body plan, allowing study of disease at early stages of embryonic development.
- 6. Ethically preferred in the drive to reduce, refine and replace.
- 7. Cost effective.

Zebrafish Heart Failure Models
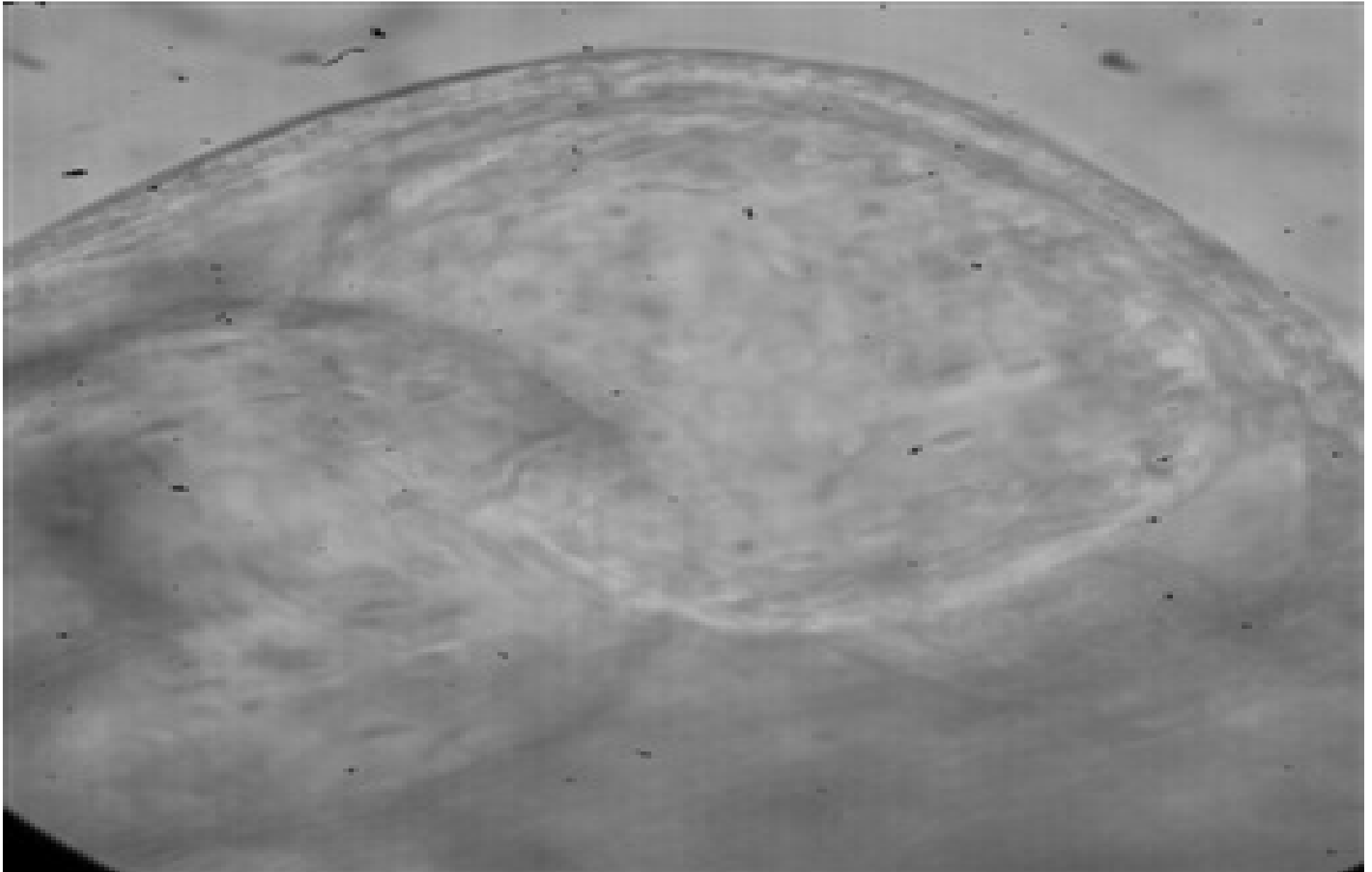

Normal

cardiomyopathy

Heart valvular disease

anemia

arrhythmia

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Control Zebrafish Heart

Zebrafish Heart Failure Model

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Carvedilol Treatment of Heart Failure Model
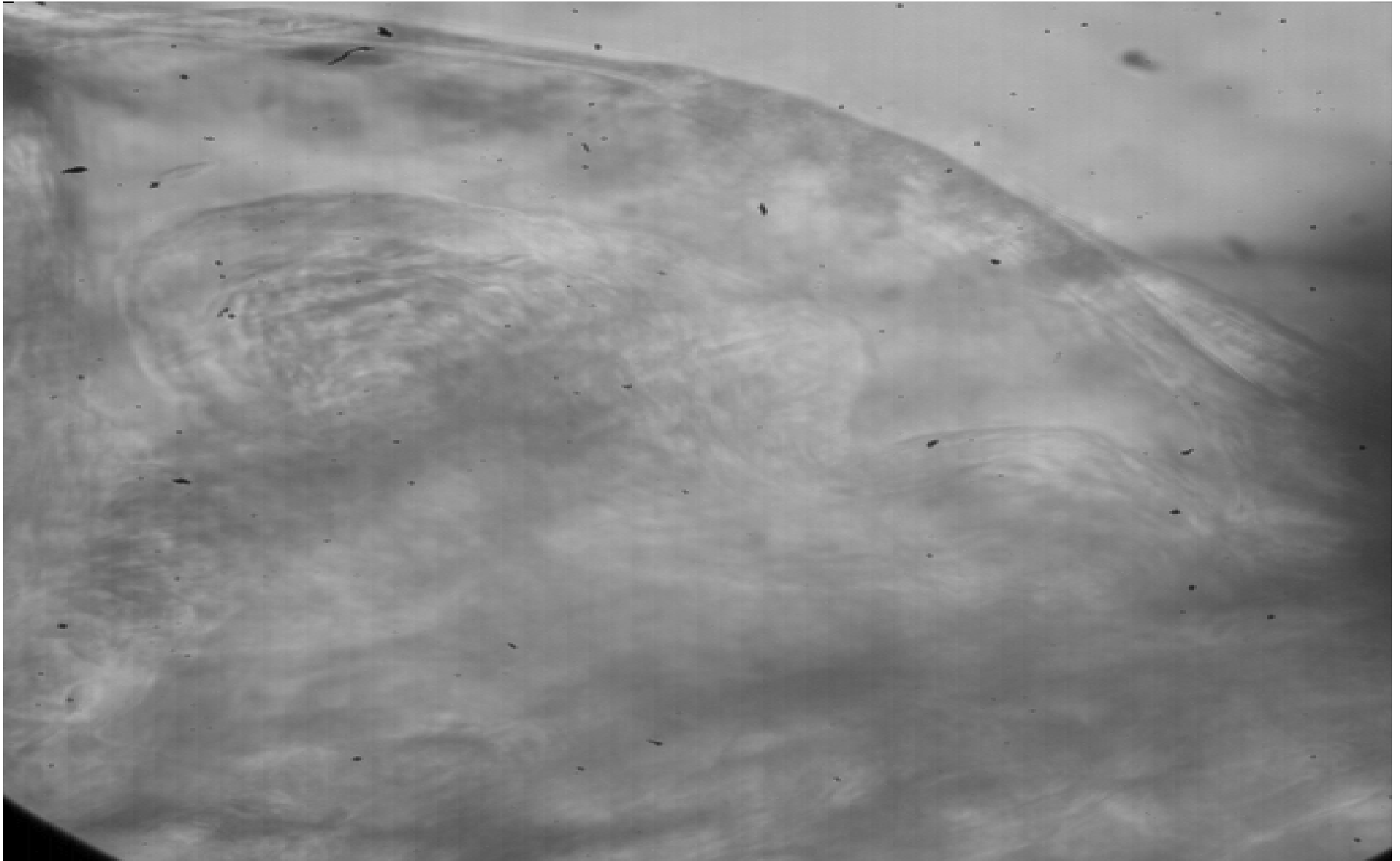

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Carvedilol Therapeutic Gene Discovery

Carvedilol

Heart failure model

After treatment

DNA micro array

Detection of therapeutic target genes by DNA Micro Array

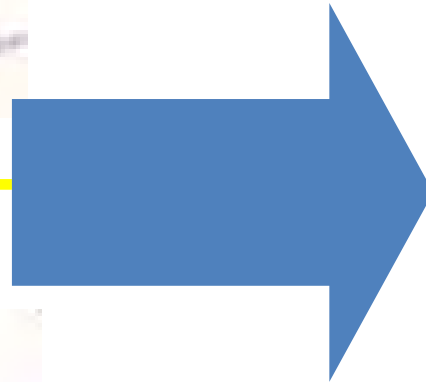Department of Molecular and Cellular Pharmacology, Pharmacogenomics and Pharmacoinformatics、Mie University Graduate School of Medicine
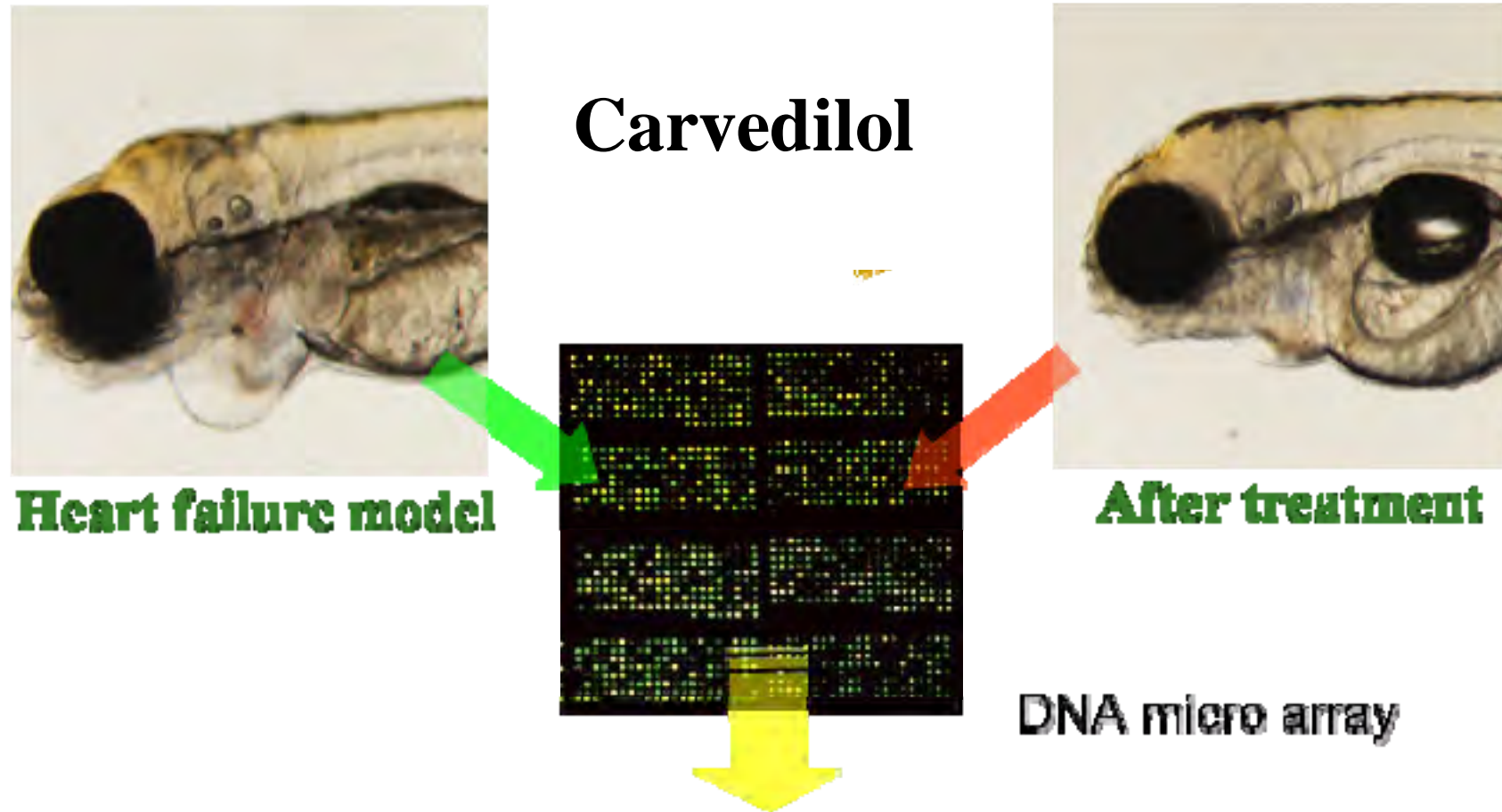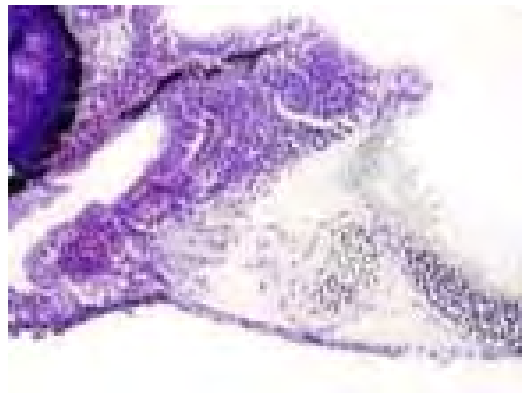
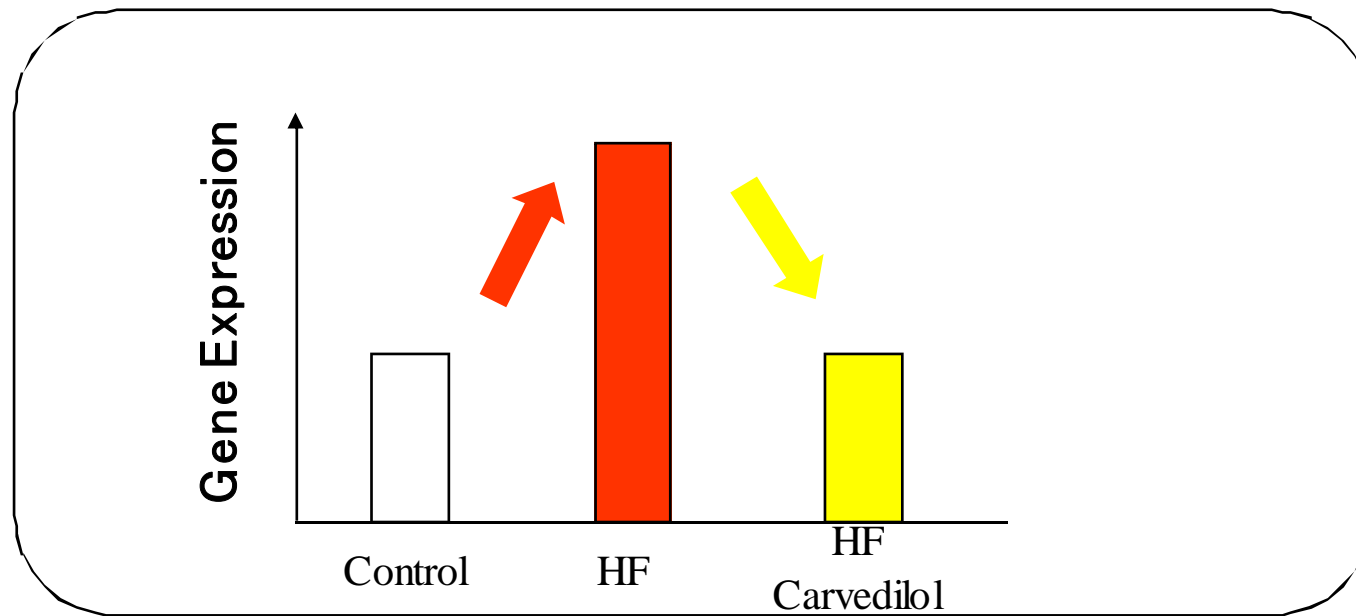# Laser-Captured Microdissection

HF

before

after

**HF
Carvedilol**
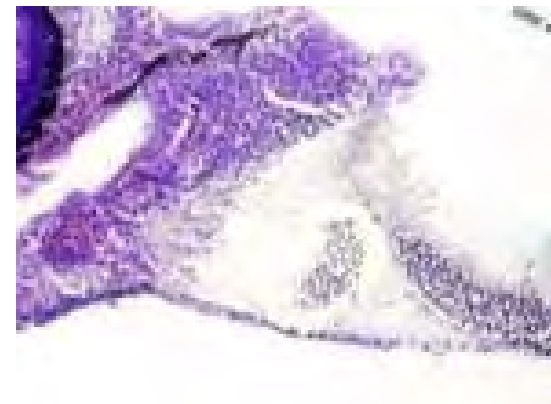
Therapeutic Gene Validation with Calvedilol
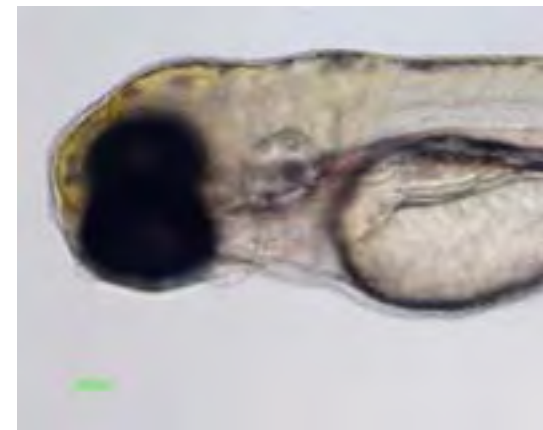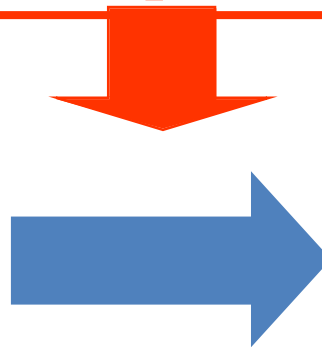
赤 : **Up by PECI kd**
緑 : **Down by PECI kd**

Fx: hypertrophy of cardiomyocytes

Fx: cell death of cardiomyocytes

STMN4

OTX2

SH3RF1

TNFRSF10B

MBIP

FASTK

GBX2

PTPRZ1

MAPK8

MAP3K12

TIA1

RNF10*

EVI1

MGST3

JNK1/2

Fx: atrial septal defect

retinoic acid

C10ORF4*

GATA4

PECI

ITGAL

TBX18

RABGGTB

Fx: area of infarct

ASNS

RARG

SPARC

TGFBR2

CCL13

PTP4A2

Fx: hypertrophy of heart cells

HAS2

NR2F1

Fx: formation of fibrous plaque

BGLAP

SP3

MYBPC3

Fx: myocarditis of rodents

Fx: dysfunction of left ventricle

Fx: myocarditis

Fx: inflammation of vasculature

LECT1

MAOB

Fx: experimental autoimmune myocarditis of rodents

Fx: calcification of cardiac valve

Fx: calcification of aortic valve

Fx: experimental autoimmune myocarditis of rats

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Forward Pharmacogenomics

Genotype

Transcriptome

Proteome

Metabolome

Phenotype

Reverse Pharmacogenomics

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