Systems Genetics to Uncover Novel Mechanisms in Heart Failure

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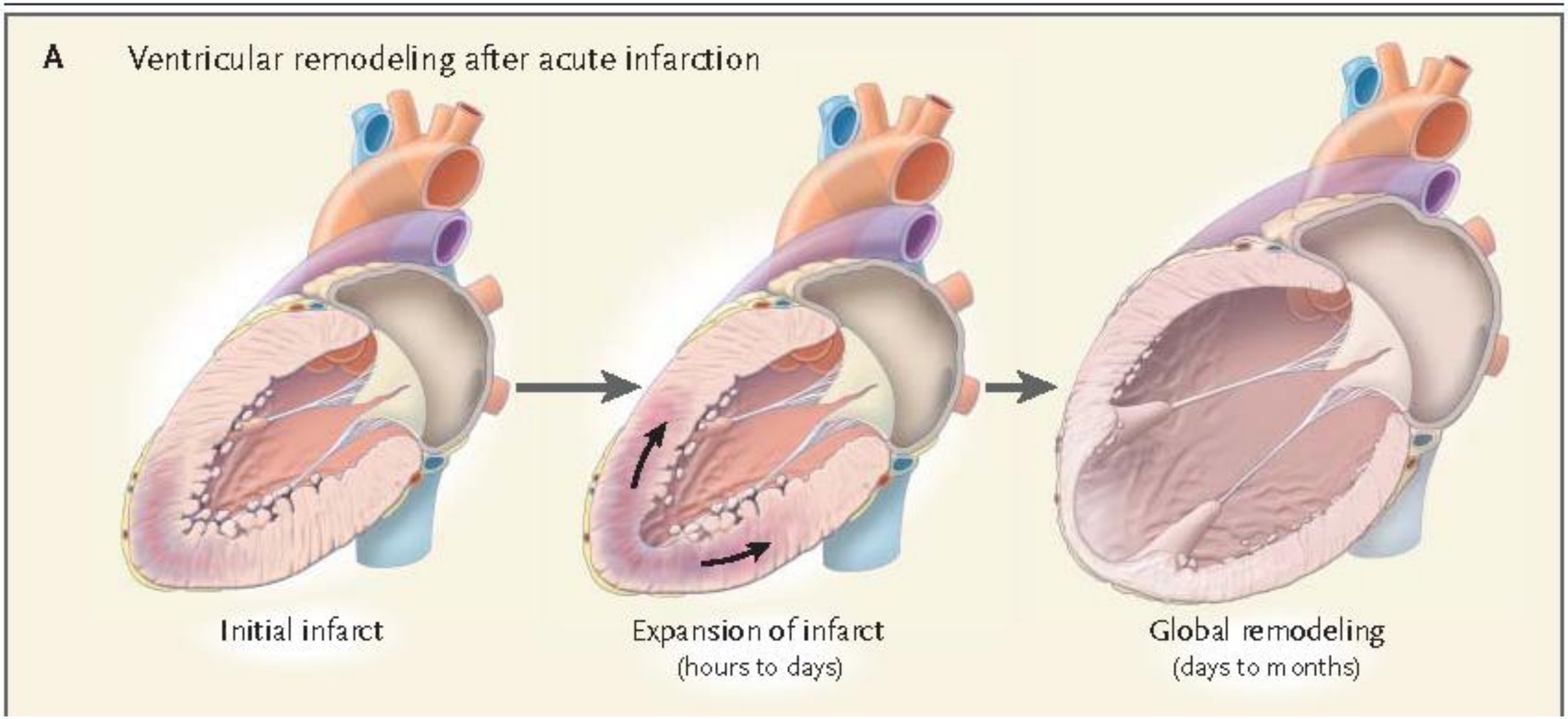
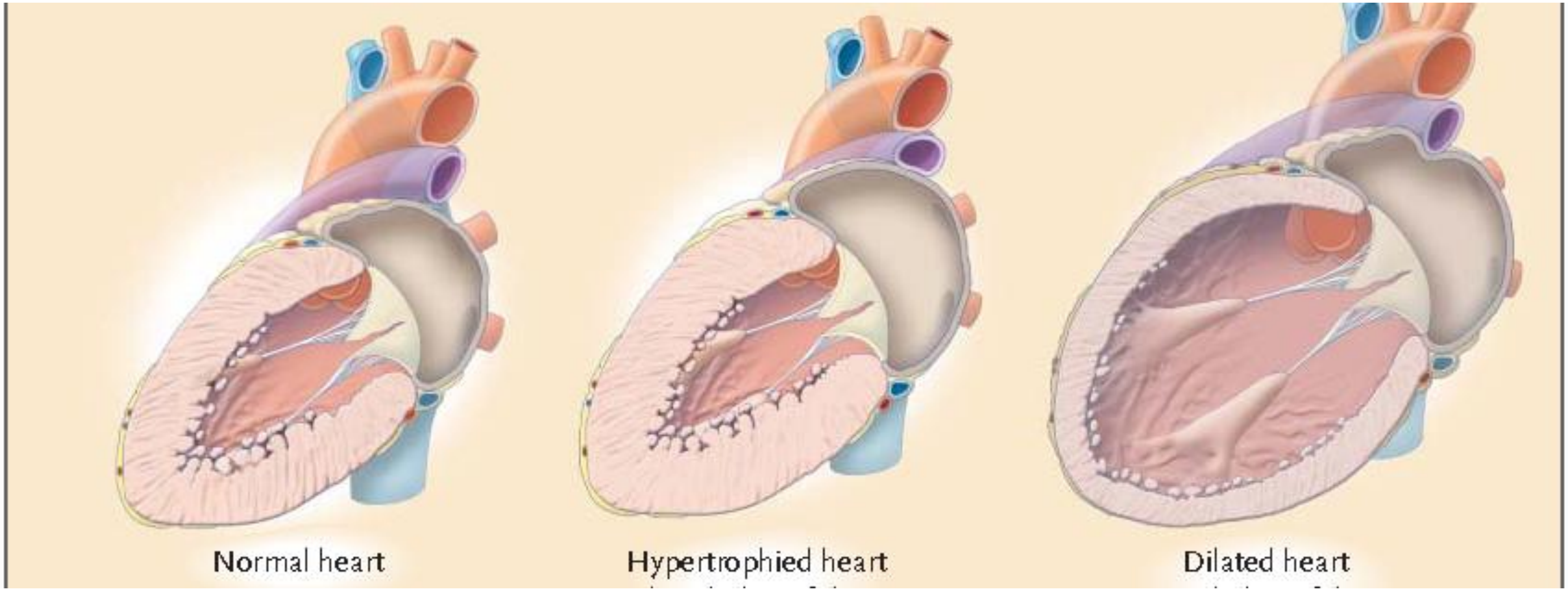
Heart Failure is a Complex Disease



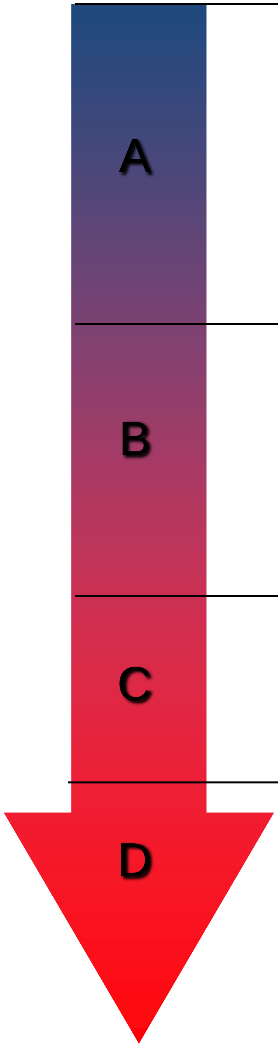
Chronic Progression Over Time

Heart Failure is a Complex Disease



- **Hypertrophic CM**
- **Dilated CM**
- **Restrictive CM**

Complexity of Heart Failure



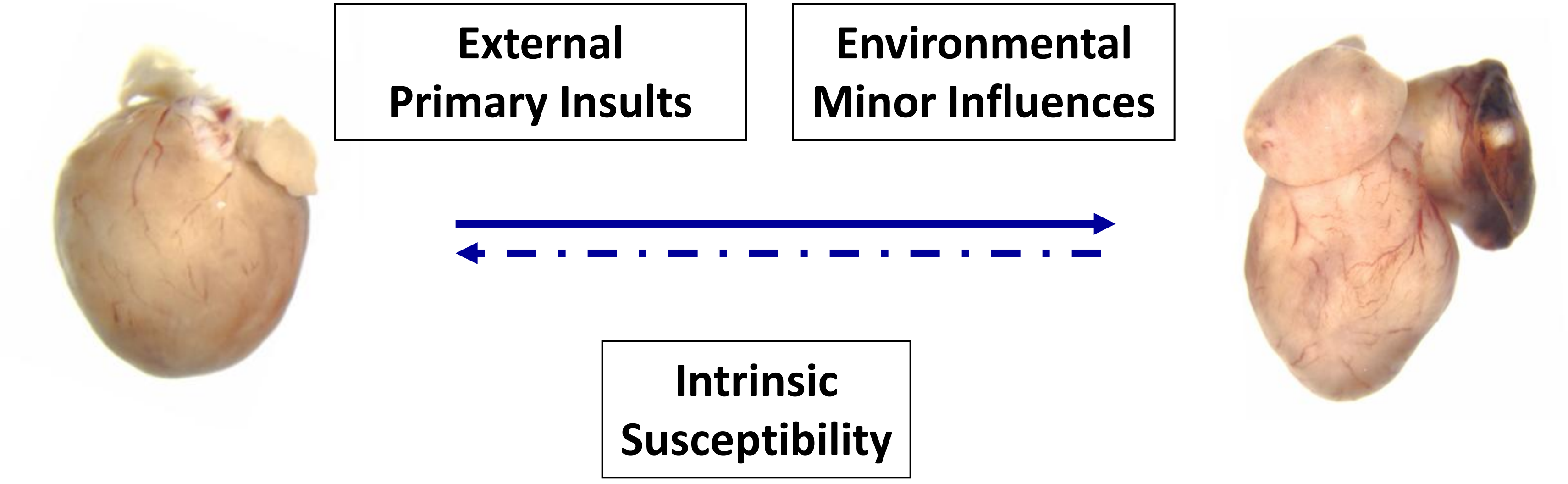
- High Risk for Developing HF
  - Diabetes Mellitus
  - Hypertension
  - Coronary Artery Disease
  - Family History of Cardiomyopathy

- Asymptomatic HF
  - Previous MI
  - LV Dysfunction
  - Valvular Disease

- Symptomatic HF
  - Known structural heart disease
  - Shortness of breath and fatigue

- Refractory End-stage HF
  - Marked symptoms at rest despite maximal medical therapy

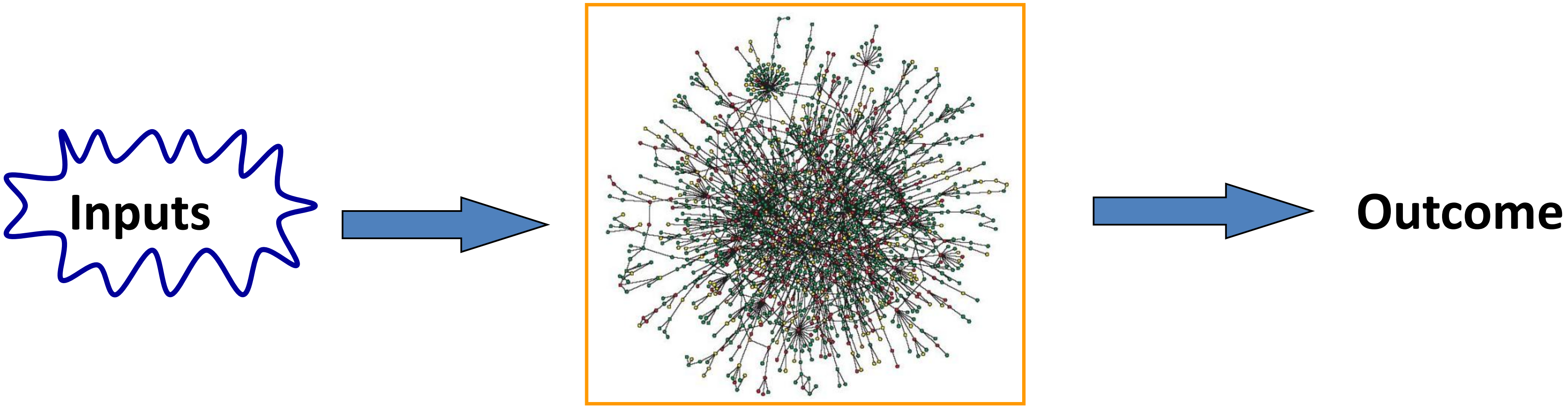
Understanding Heart Failure as an Intact System



External Primary Insults

Environmental Minor Influences

Intrinsic Susceptibility

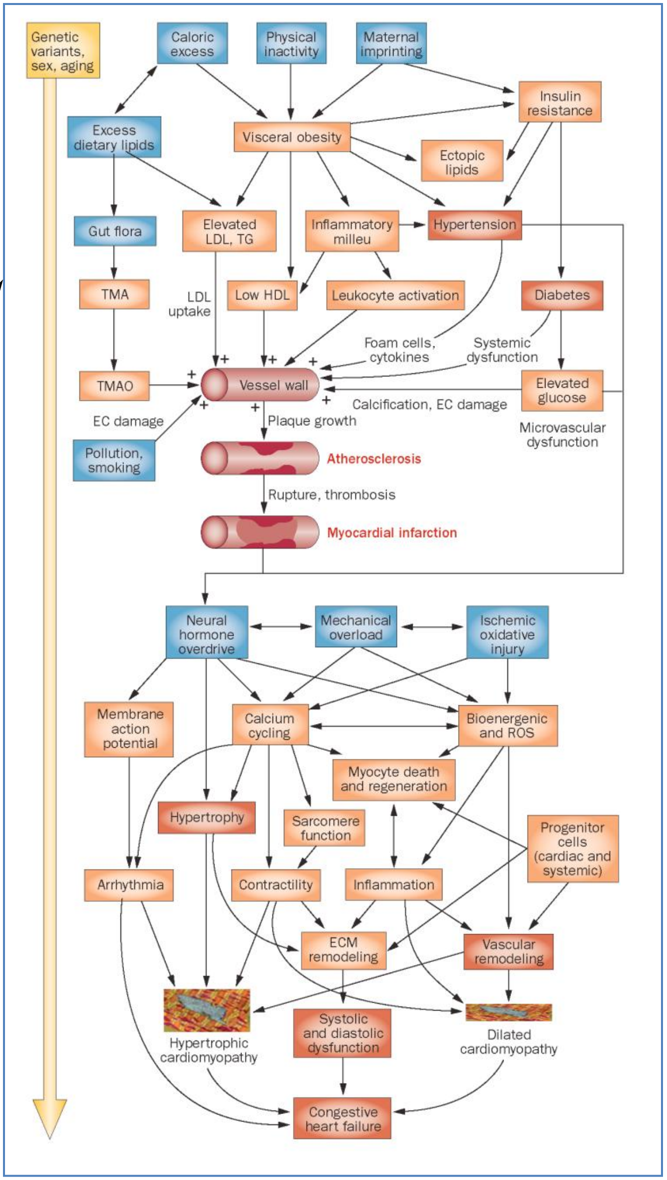


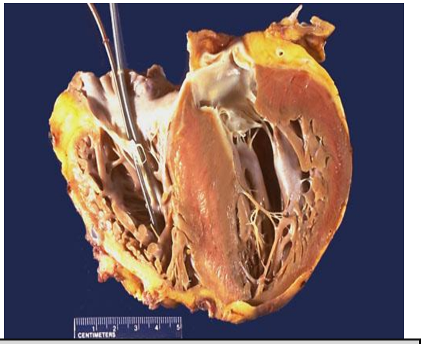
Inputs

Outcome

Grand Challenges in Heart Failure Research

stress





Myocyte Hypertrophy, Death, ECM, Transcriptome, Metabolic, Electro/physiological and Vascular Remodeling

Grand Challenges in Heart Failure Research

stress

Signaling Components

Diversity of signaling components:

Genes, Proteins, PTM, miRNA, lipids - - -

Dynamics of signaling interactions:

Proteins complexes, intracellular localization and traffic - - -

Interactions

Non-linear interaction of different components

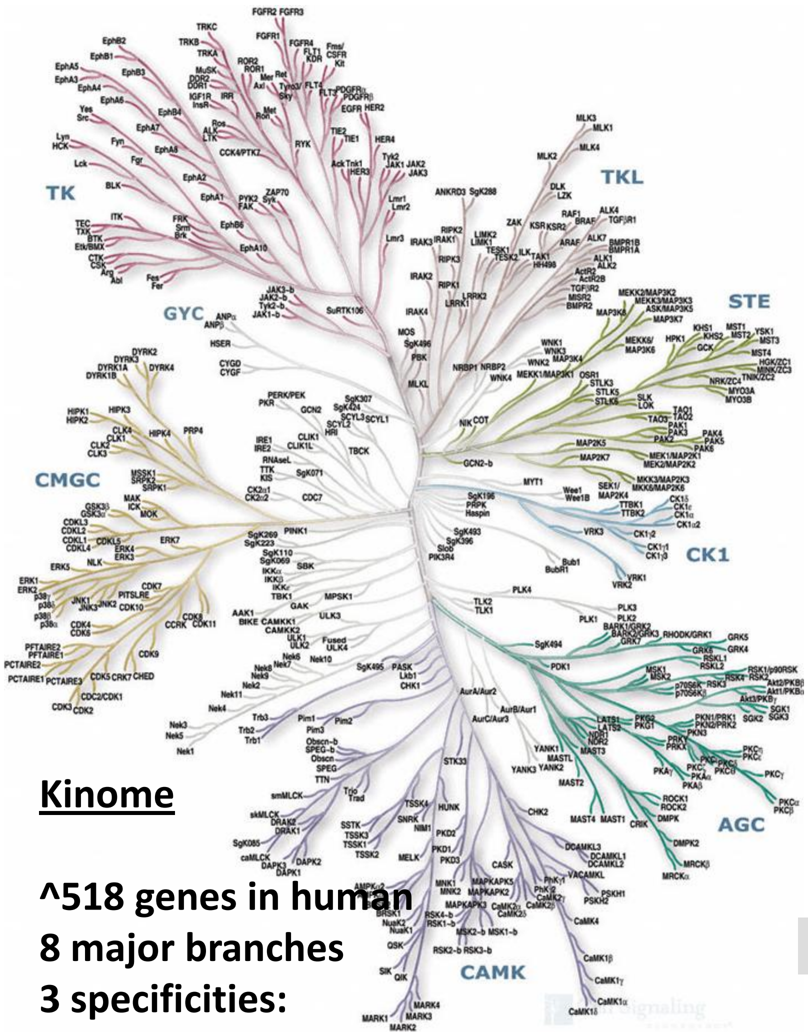
Quantitative properties vs qualitative outcomes

Molecule - Cell - Tissue - Organ
Scale of Complexity

Network Systems

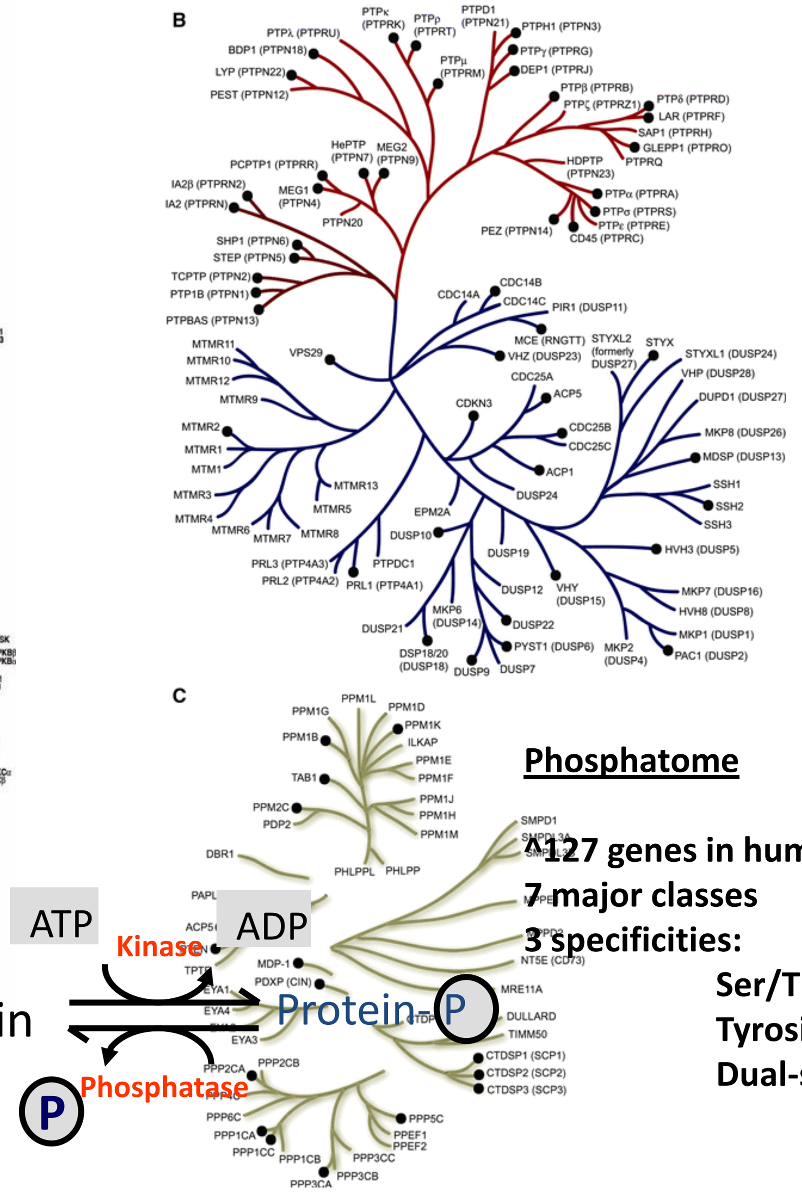
Myocyte Hypertrophy, Death, ECM, Transcriptome, Metabolic, Electro/physiological and Vascular Remodeling

Kinome vs. Phosphatome



Kinome

^518 genes in human
8 major branches
3 specificities:
Ser/Thr kinases
Tyrosine Kinases
Dual-Kinases



Phosphatome

^127 genes in human
7 major classes
3 specificities:
Ser/Thr (20)
Tyrosine (96)
Dual-specific (11)

Grand Challenges in Heart Failure Research

stress

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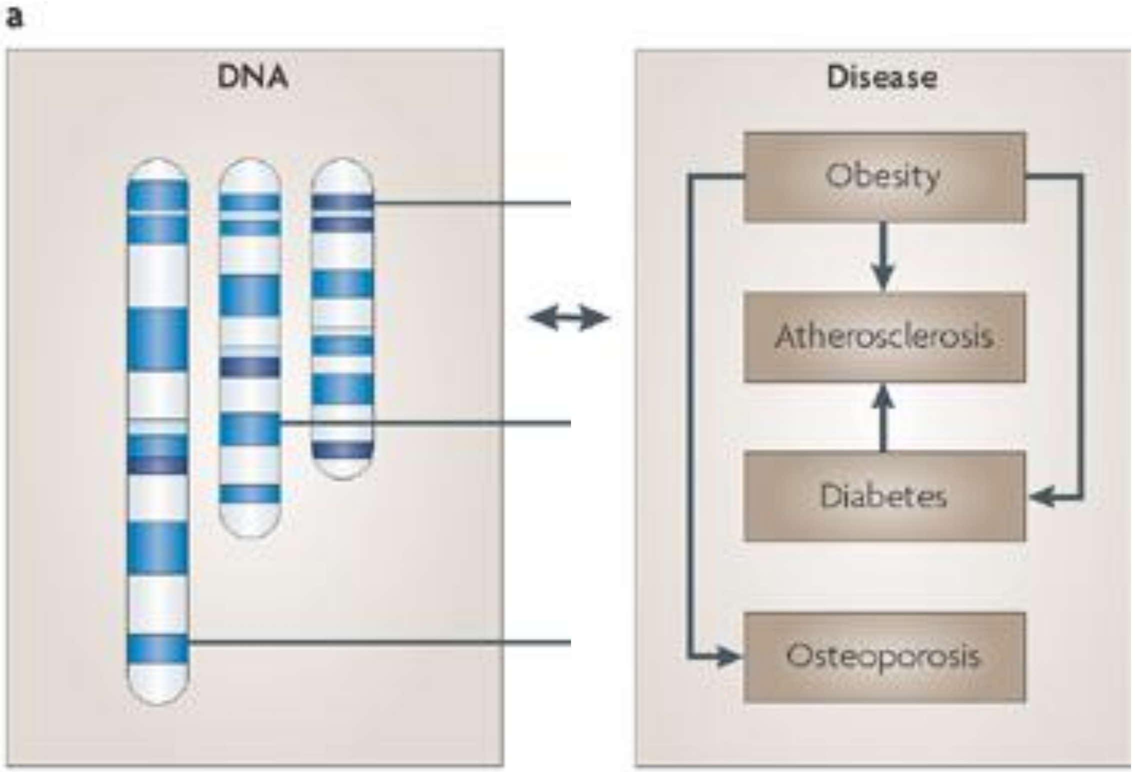
Myocyte Hypertrophy, Death, ECM, Transcriptome, Metabolic, Electro/physiological and Vascular Remodeling

GWAS: From Genetic Variants to Disease Causal Genes

QTLs



Limitations: False Positives, Lack of Mechanistic Content, Ineffective for Complex Traits

A Systems Approach for Complex Human Diseases

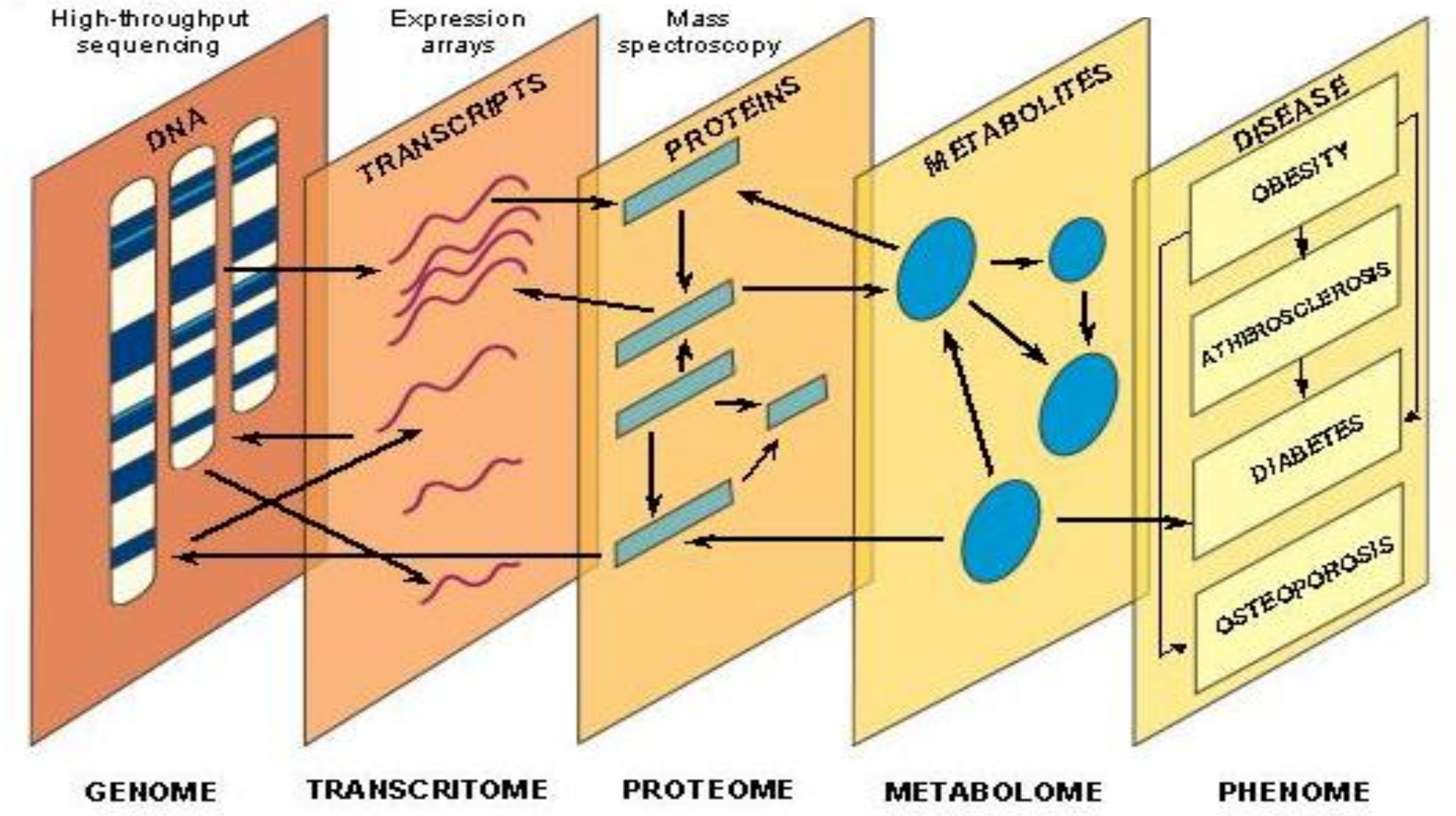
High Density SNP Chips

Whole-Genome

Whole-Genome Yeast Two-Hybrid Screens

Mass Spectroscopy

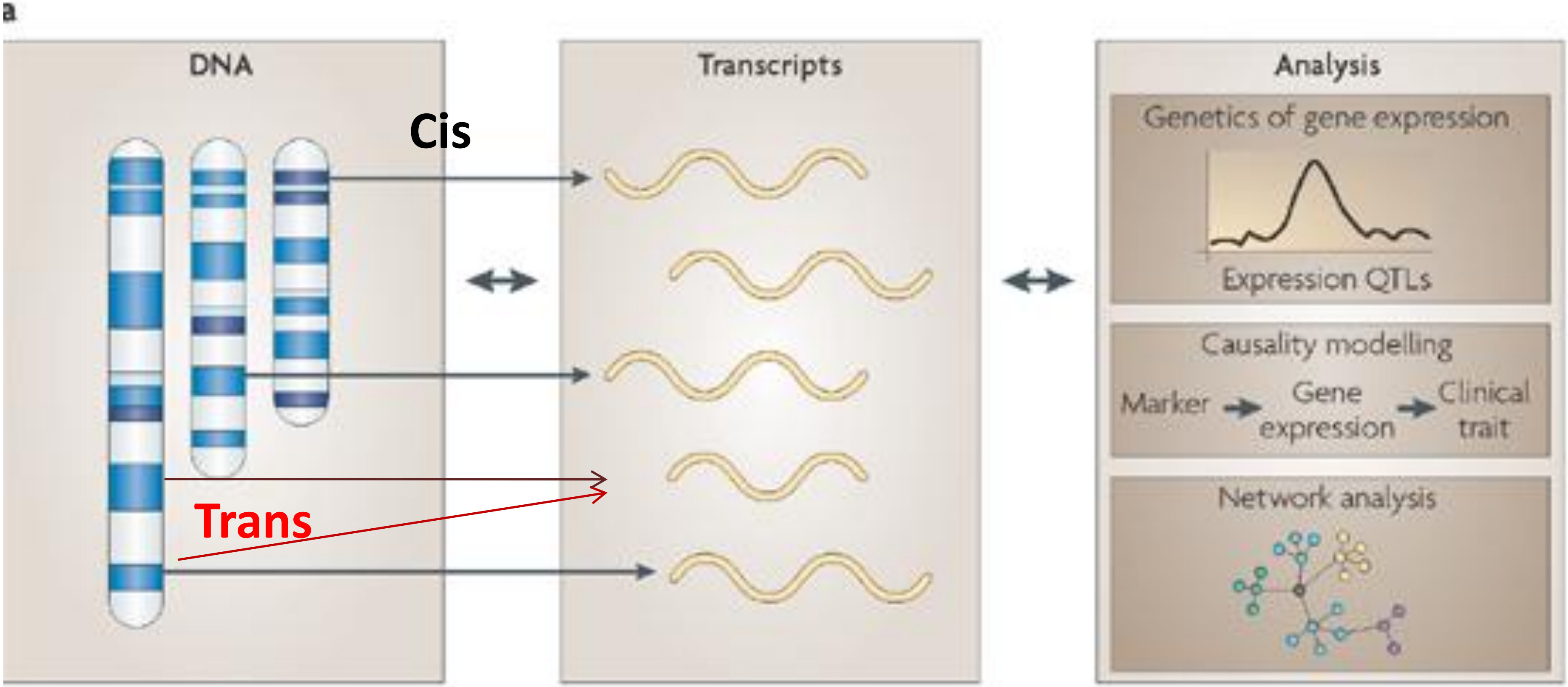
Clinical Data Imaging (NMR, PET)



Farber and Lusis, 2008

Systems + Genetics

From genetic variants to eQTL （Expression Quantitative Trait Locus）



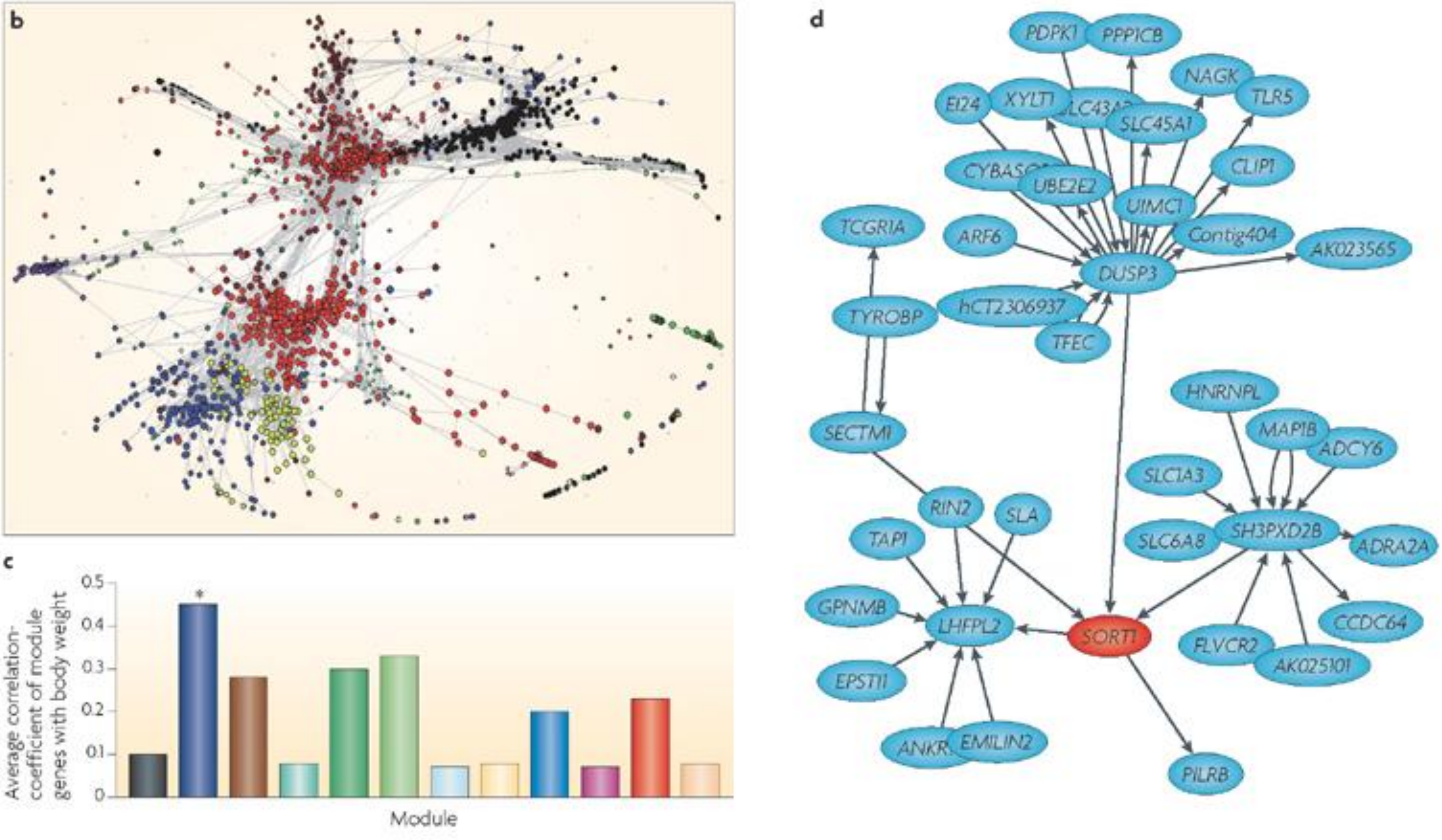
Others：

eQTLs
mRNA Expression

pQTLs
Protein Expression

mQTLs
Metabolic Profile

Systems Genetic to Uncover Gene Modules in Human Endothelial Cells



Lusis， Nature Review

Systems Genetics for Complex Diseases

Key to Success:

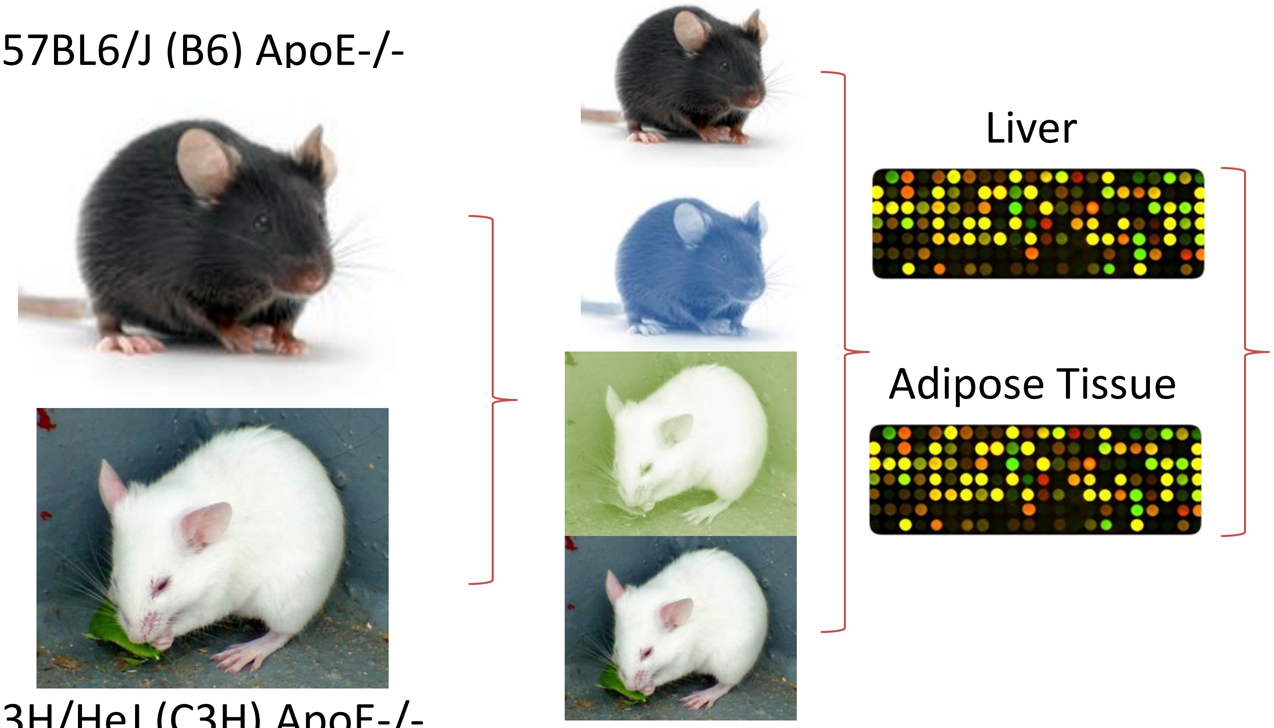
1). Stable but Diverse Genetic Population (large number of inbred strains)
2). High-resolution genotype mapping
3). Quantifiable clinical traits
4). High-throughput Omics: genomics, proteomics, metabolomics
5). Bioinformatics

Vol 452|27 March 2008|doi:10.1038/nature06757 nature

ARTICLES

Variations in DNA elucidate molecular networks that cause disease

Yanqing Chen[1]*, Jun Zhu[1]*, Pek Yee Lum[1], Xia Yang[1], Shirly Pinto[2], Douglas J. MacNeil[2], Chunsheng Zhang[1], John Lamb[1], Stephen Edwards[1], Solveig K. Sieberts[1], Amy Leonardson[1], Lawrence W. Castellini[3], Susanna Wang[3], Marie-France Champy[6], Bin Zhang[1], Valur Emilsson[1], Sudheer Doss[3], Anatole Ghazalpour[3], Steve Horvath[4], Thomas A. Drake[5], Aldons J. Lusis[3,4] & Eric E. Schadt[1]



C57BL6/J (B6) ApoE-/-

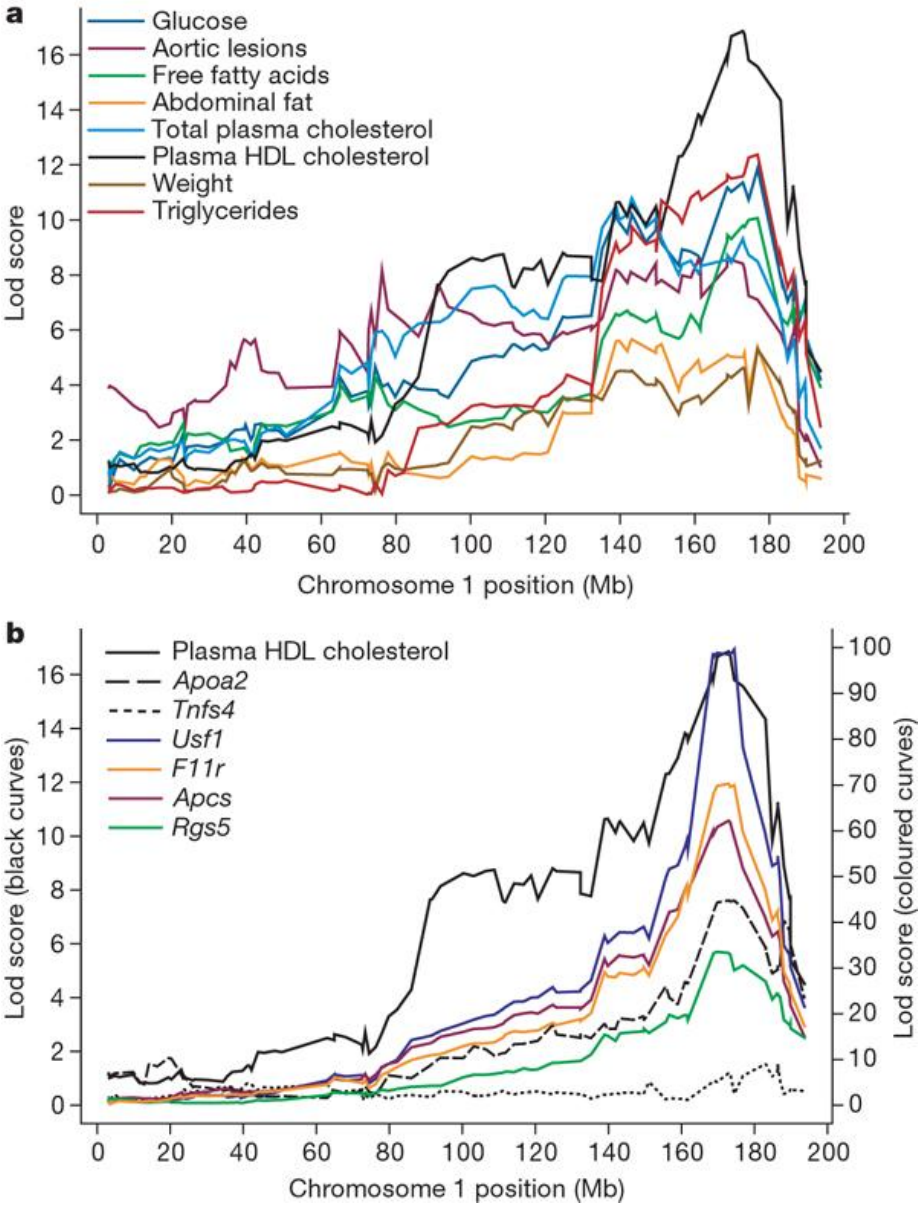
C3H/HeJ (C3H) ApoE-/-

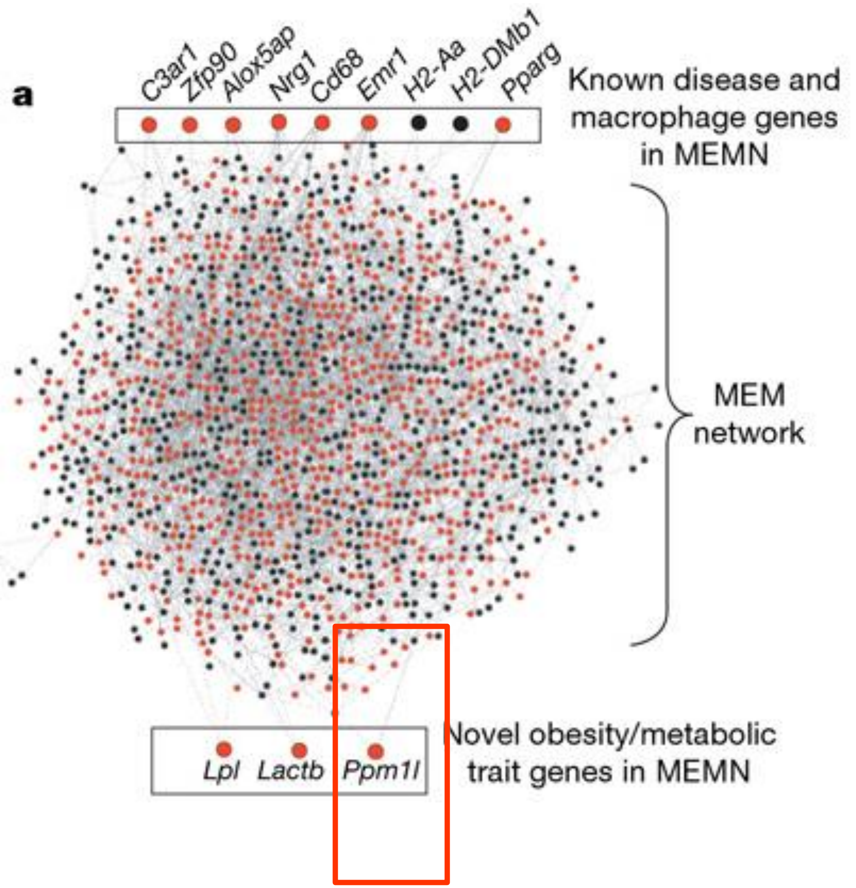
Liver

Adipose Tissue

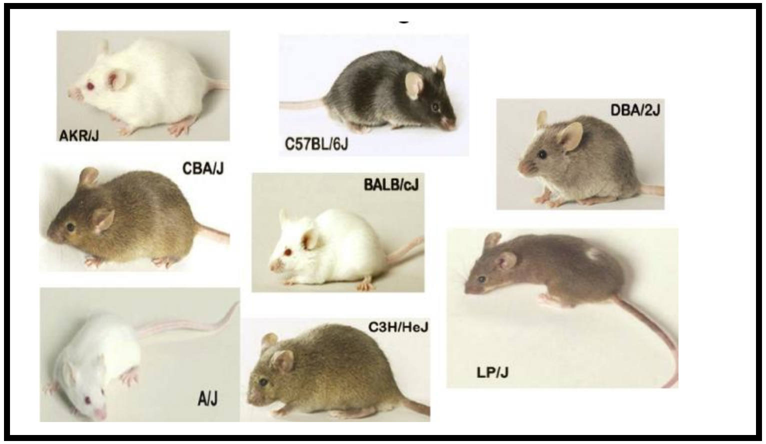
Metabolic Profile

Macrophage Expression Metabolic Network





Hybrid Mouse Diversity Panel (HMDP)

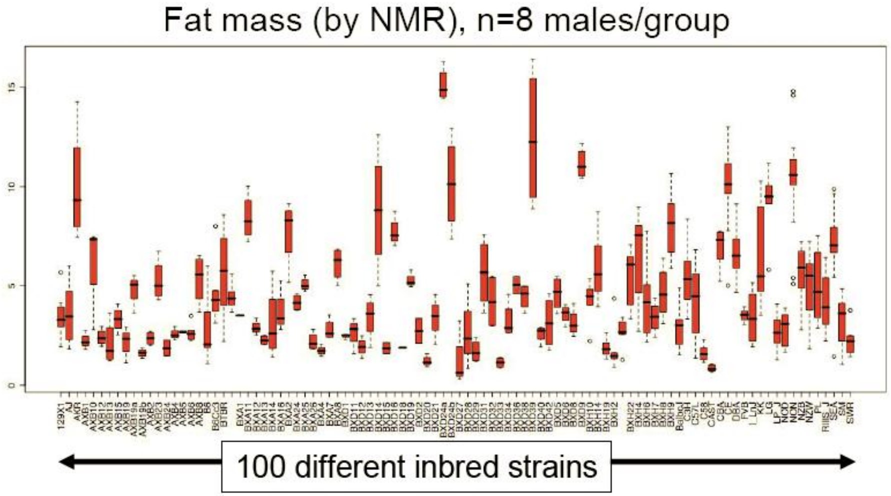


~100 "classical" inbred and recombinant inbred strains

- ◆ Most strains fully sequenced
- ◆ ~ 11 million SNPs
- ◆ > 10,000 functional variants

Data collection:
Phenomic
Transcriptomic
Proteomic
Metabolomic

Whole genome association
Systems genetics

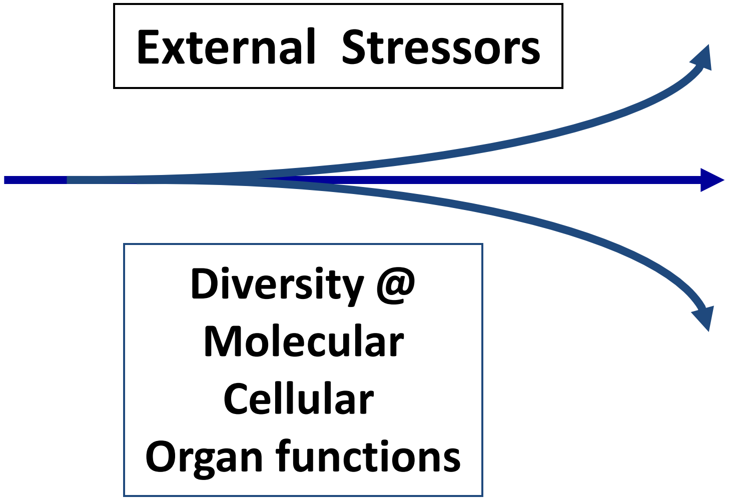

Fat mass (by NMR), n=8 males/group

100 different inbred strains

Bennett et al. Genome Res 2010

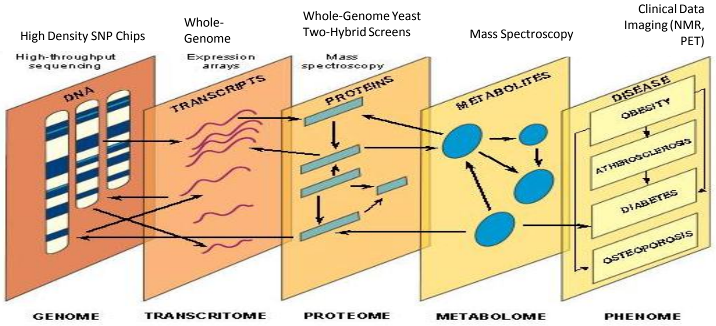
Systems Approach for Complex Human Diseases

Genetic Diversity
Within Individual Species

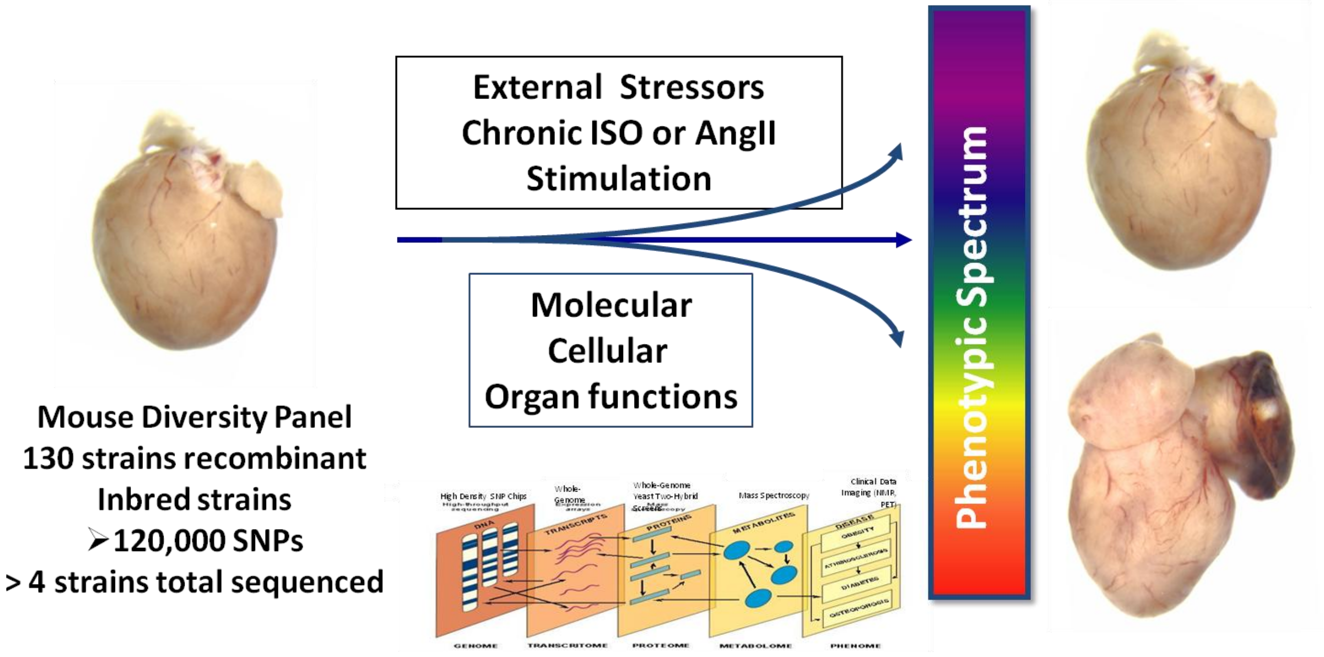


External Stressors

Diversity @
Molecular
Cellular
Organ functions



Basic Elements in Systems Genetics for Heart Failure



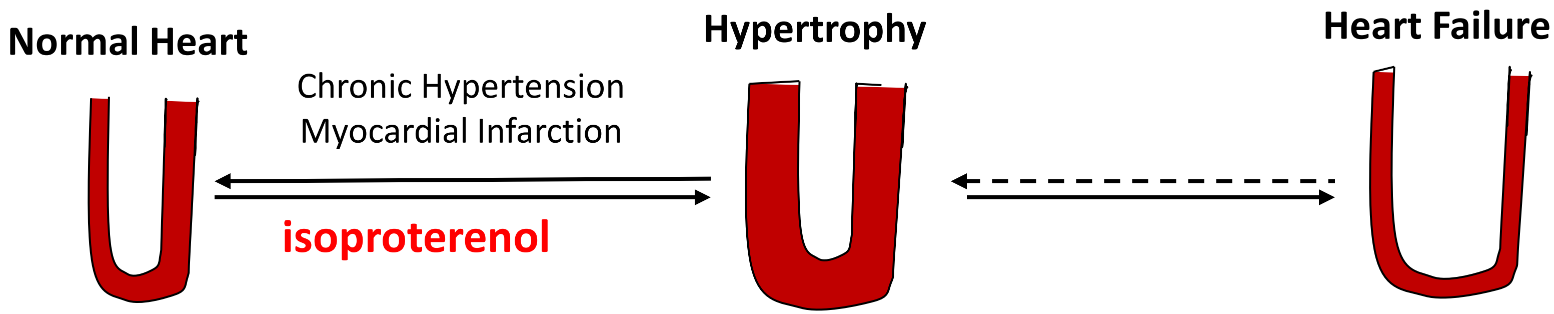
External Stressors
Chronic ISO or AngII
Stimulation

Molecular
Cellular
Organ functions

Mouse Diversity Panel
130 strains recombinant
Inbred strains
➢120,000 SNPs
> 4 strains total sequenced

1. HMDP animals and disease related injury (ISO minipump)
2. Robust high-throughput functional characterization (Echo)
3. High-throughput molecular/cellular analysis (Genomic Core)
4. Unbiased bioinformatic analysis to establish causal genes and networks
5. Clinical Validation

β-AR Agonist model of heart failure



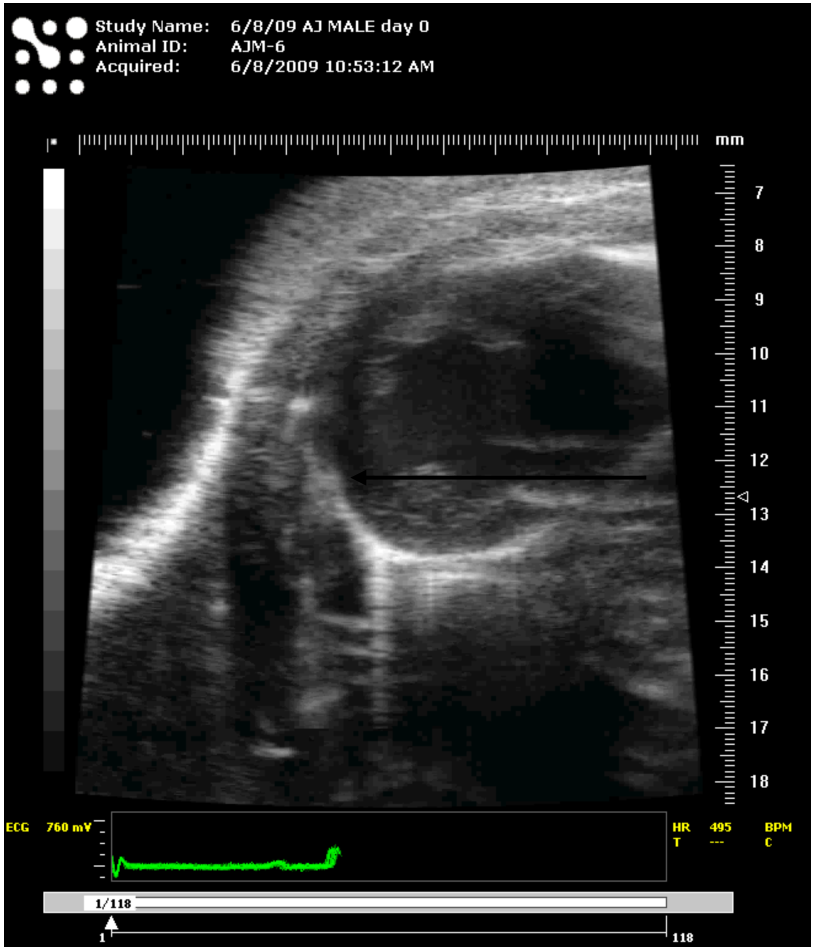
Normal Heart

Hypertrophy

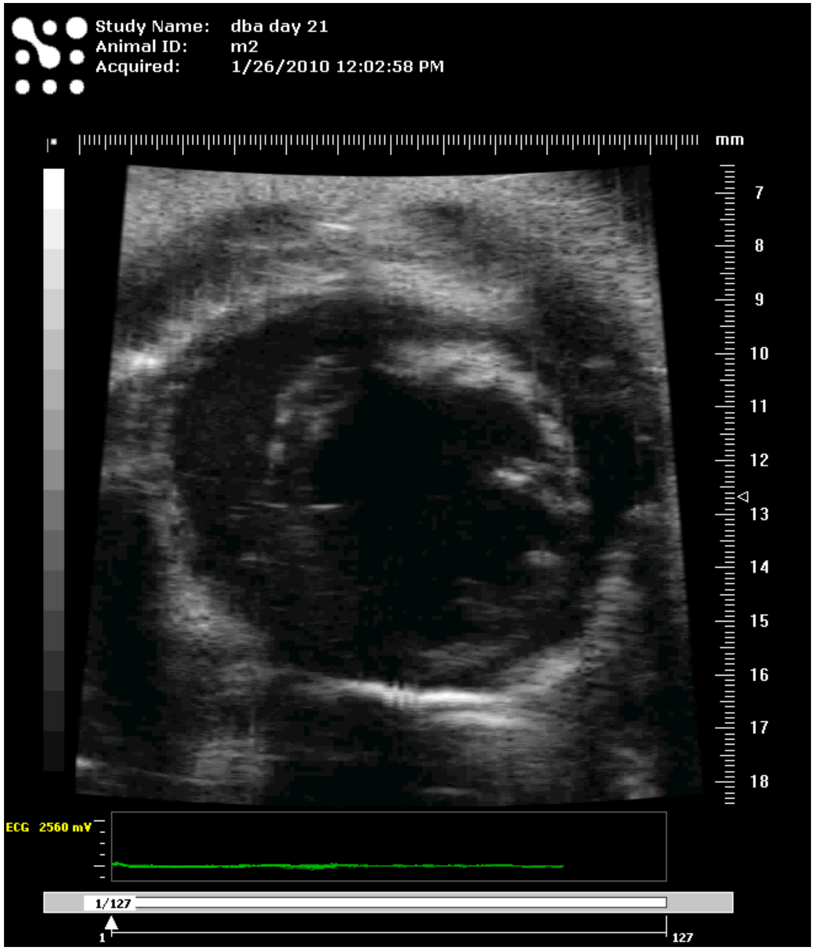
Heart Failure

Chronic Hypertension
Myocardial Infarction

isoproterenol

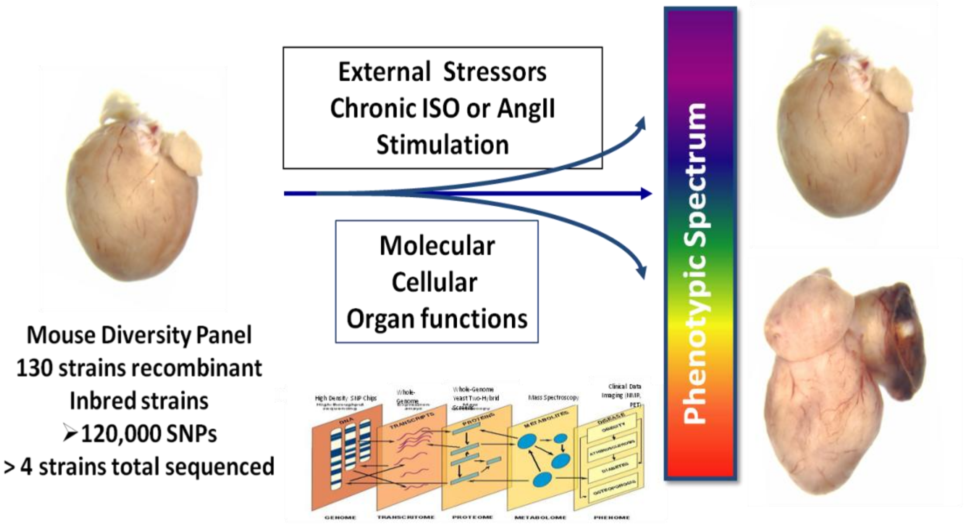


Study Name: 6/8/09 AJ MALE day 0
Animal ID: AJM-6
Acquired: 6/8/2009 10:53:12 AM



Study Name: dba day 21
Animal ID: m2
Acquired: 1/26/2010 12:02:58 PM

Potential Implications



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Human Translation

1. Disease causal genes and networks as diagnostic and therapeutic targets
2. Disease stratification and personalized medicine
3. Better therapeutic goals

Heart to Heart Thanks!

Lab Members

Current:

Vincent Ren, Hongmei Ruan, Jing Gao, Haiying Pu, William Foster, DeAnna Steiger, Erik Anderson, Jim Oheven, Chen Gao, Marlin Tourma, Zhihua Wang,

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