At the “Heart” of the JI: Cardiology Past, Present and Future

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3 sticks of Incense- Past, Present, and Future
CARDIOLOGY PAST
Michigan Medicine and PKUHSC
Historical Institutions in Cardiovascular Disease
Diagnosis and Treatment

• Exemplar contributions of PKUHSC in cardiology/cardiac surgery

• Exemplar contributions of Michigan Medicine in cardiology/circulation
PKUHSC Cardiovascular Landmarks

• Establishment of CCU in 1978 (one of the first in China)
• Early adoption of rotoblator technology
• First ablation of atrial tachycardia (1983)
• First coronary stent in China (1993)
• Current leading center for CABG in China
Development of the ECG: Frank Wilson, *circa* 1925-40

METHODS AND APPARATUS

of leading referred to is illustrated in Fig. 1. Electrodes are placed on the right arm, left arm, and left leg, in exactly the same manner as in the preceding diagram illustrating the method of leading used to record the potential of a single electrode. Electrodes on the right arm (R), left arm (L), and left leg (F) are connected through equal resistances of 5,000 ohms to a single stage D.C. amplifier. The central terminal and an exploring electrode, or one of the electrodes as indicated here, are connected to the input terminals of a voltmeter with a balanced plate circuit in which the string galvanometer

Scheme for direct measurement of potentials.

$R = 5000 \text{ ohms}$
The earliest cardiology journals: 1891-1913

Figure 20 Title page of Volume I, No. 1 of Heart, the first cardiology journal in the English language.
CCU/Telemetry: Galvanometer Room, UM Heart Station, circa 1950
Extracorporeal Membrane Oxygenation (ECMO) - Bob Bartlett
Mineralocorticoid receptor blockade for the treatment of heart failure - Bertram Pitt

Spironolactone

Eplerenone
JI Cardiovascular Programs: 9 years and counting

- combined ≈ $6M (35M 人民币) investment in our future
- $10M external funding and counting
- 20,000 research subjects/samples and counting
- 35 papers and counting
- dozens of friendships
Cardiovascular #1 (HDL)

Project title: Dysfunctional HDL and Cardiovascular Disease (Co-PIs: Eugene Chen, M.D., Ph.D., Guisong Wang, M.D.)

Significant Outcomes:
• Trainees mentored by Co-PIs:
  • 3 PKUHSC faculty mentored at Michigan by Drs. Chen and Pennathur.
  • 3 Michigan residents clinical rotation at PKUHSC mentored by Drs. Gao and Wang.
• 4 peer-reviewed publications
  PLoS ONE
  Am J Physiol Cell Physiol
  J Clinical Invest.
• Extramural funding of $2,821,885:
  NIH R01 -HL134569 (3/2017 to 02/2021)
Cardiovascular #2 (Myocardial Infarction)

Project title: Finding genes for myocardial Infarction and blood lipid levels in a Chinese sample from Beijing

(Co-PIs: Cristen Willer, Ph.D., Wei Gao, M.D., Ph.D., Ming Xu, Ph.D.)

Significant Outcomes:

- 8,621 samples from 4 hospitals collected for genotyping.
- Identified 3 novel lipid variants in Asians.
- Discovered new genes involved in blood cholesterol levels; one increases risk of fatty liver disease.
- Three peer-reviewed papers
  - Journal of Human Genetics (2014)
Cardiovascular #3 (Hypertension)

Project title: Blood pressure and hypertension genetics
(Co-PIs: Santhi K. Ganesh, M.D. & Yan Zhang, M.D.)

Significant Outcomes:
- 10,000 samples were collected for genotyping
- Generated a mouse null for the CCDC93 gene
- 3 PKUHSC junior faculty mentored at UM by Dr. Ganesh
- One peer-reviewed paper
  Am J. Hum Genet. (2014)
Cardiovascular #4 (Air Pollution)

Project title: Particulate matter air pollution and high density lipoprotein dysfunction
(Co-PIs: Robert D. Brook, M.D., Jianping Li, M.D., Wei Huang, M.D.)

Progress:
• Both studies at PKUHSC and Michigan Medicine have been successfully completed.
• Initial results demonstrate adverse effects of air pollutants on several cardiovascular parameters in Beijing, particularly among overweight participants.
• Blood biomarkers analyses ongoing to assess HDL function.
• Five papers:
  Circulation (2017)
  Am. J. Hypertens (2018)
  American Journal of Cardiology (2018)
  Global position statement on air pollution & cardiovascular disease (in process).
Cardiovascular #5 (Atrial Fibrillation)

Project title: Molecular Mechanisms of Fibrosis and Progression from Paroxysmal to Persistent Atrial Fibrillation (Co-PIs: Jose Jalife, M.D., Jihong Guo, M.D., Ph.D., Xuebing Li, M.D.)

Progress:

• >55 patients with either paroxysmal or persistent atrial fibrillation recruited and being followed
• Dr. Yoshio Takemoto awarded the 2016 Young Author Achievement Award by the American College of Cardiology for his JI paper.
• Continuing study of cardiac fibrosis and electrical remodeling in the transition from paroxysmal to persistent atrial fibrillation.
• One Michigan resident did one-month clinical rotation mentored by Dr. Li.
• Two PKUHSC PhD graduates were mentored by this project.
• Grant from the Chinese National Natural Science Foundation
Cardiovascular #6 (Acute Aortic Dissection)

Project title: Identify Smooth Muscle Cell Specific Protein as Biomarkers for Early Diagnosis of Acute Aortic Dissection
(Co-PIs: Bo Yang, M.D., Ph.D., Zhe Zhang, M.D.)

Progress:
- 104/310 patients have been enrolled to Identify elevated proteins in the serum in patients of acute aortic dissection (AAD) using proteomics.
- Identified three target proteins as biomarkers of acute aortic dissection with proteomics.
- Completing collection of the blood samples of patients with acute aortic dissection
Cardiovascular #7 (Intracerebral hemorrhage)

Project title: Qualitative Measurements of Brain Iron Overload After intracerebral Hemorrhage  
(Co-PIs: Guohua Xi, M.D., Yining Huang, M.D.)

Progress:
- 30/48 ICH patients enrolled for MRI imaging analysis to define the relationship between early hemolysis and perihematomal edema.
- One PKUHSC faculty received extensive training at Michigan Medicine’s Crosby Neurosurgical Laboratories from Feb 2016 to Jan 2017.
- Extramural funding: $2.785M from NIH.
- Multiple peer-reviewed publications:
  - Transl Strok Res.
  - Experimental Neurology
  - Stroke.
Cardiovascular #8 (Atherosclerosis)

Project title: The Role of Hematopoietic Factors in Atherosclerotic Vascular Diseases
(Co-PIs: Santhi Ganesh, M.D., Yan Zhang, M.D.)

Progress:
• EPO (erythropoietin) measurement completed at PKU for 5,000
• Analysis of blood cell traits completed:
  Novel variant association with platelet count.
• One paper published:
  Nature Genetics
  3 more additional in preparation
Cardiovascular #9 (Cell Therapy)

Project title: A Chemical Approach to Generating Patient-Specific Cardiac Stem Cells for Cell Therapy Against Cardiovascular Disease (Co-PIs: Zhong Wang, Ph.D., Hongkui Deng, Ph.D.)

Progress:

- Mastered the technique for chemical induced mouse iPSCs and characterize the mouse iPSCs to cardiac lineages
- Derive embryonic stem cell lines or induced pluripotent stem cell lines that are able to contribute both embryonic and extra-embryonic lineages
- Transplantation of ESC/iPSC derived cardiac progenitor cells and cardiomyocytes into infarcted animal hearts.
- Exploring to repurpose a FDA proved drug in treating acute heart attack
- Seven papers have been published in the following peer-reviewed journals: Acta Biomaterialia., J Stem Cell and Transplantation Biology, Curr Opin Organ Transplant, Cell Discovery, Am J Transl Res., Cell, Stem Cell Res. Ther.
Cardiovascular #10 (Aortic Aneurysm)

Project title: Multi-ethnic study of genetic risk factors to discover mechanisms of aortic aneurysm and dissection  
(Co-PIs: Cristen J. Willer, Ph.D. & Zhe Zhang, M.D.)

Progress:
• 75 cases have been enrolled and collected.
• Data continues to be collected for near-term manuscript preparation.
Cardiovascular #11 (ENVOY Clinical Trial)

Project title: Evaluation of spironolactone Versus indapamid on target organ damage in patients with Obesity and Hypertension (ENVOY) (Co-PIs: Betram Pitt, M.D., & Guisong Wang, M.D.)

Progress:

• IRB approval at PKUHSC received in June 2018.
• Ongoing project collaboration.
Cardiovascular #12 (Antiplatelet Therapy)

Project title: Overcoming Racial Disparity in Antiplatelet Therapy
(Co-PIs: Daniel Eitzman, M.D., & Jianping Li, M.D.)

Progress:
• IRB approval at PKUHSC received in May 2018.
• Ongoing project collaboration.
• Study team has developed an obese, insulin resistant murine model in which the effects of clopidogrel and DT-678 can be tested towards clinically relevant endpoints of both platelet aggregation and arterial thrombosis. This finding is clinically important considering millions of obese patients are treated with clopidogrel.
Cardiovascular #13 (Cardiac Injury)

Project title: β-adrenergic Receptor in Cardiac Injury and Atherosclerotic Plaque Stability: Role of NADPH Oxidase 4 (NOX4)
(Co-PIs: Marschall Runge, M.D., Ph.D. & You-Yi Zhang, M.D.)

Progress:
- New JI award.
- IRB submission approved at Michigan Medicine and PKUHSC.
Cardiovascular #14 (HFrEF, ALDH2)

Project title: Evaluation of the Efficacy of Spironolactone on HFrEF Patients with ALDH2 Deficiency (Co-PIs: Porama Thanaporn, MD, Bertram Pitt MD & Wei Gao, MD)

Progress:
- New JI award.
- IRB submission in progress at Michigan Medicine and PKUHSC.
CARDIOLOGY PRESENT
Cardiology: An imaging revolution

- Electrical imaging of the heart
  - NOGA /Electroanatomic mapping

- Metabolic imaging of the heart
  - Cardiac positron emission tomography

- Inflammatory Imaging of the heart
  - Metabolic tracers

- Predictive imaging of the heart
  - OCT, predictive plaque rupture

- Functional Imaging
  - Echo, MR, CT
Cardiac imaging

- Scintigraphic imaging
- Antimatter imaging
- Sonographic imaging
- Magnetic Resonance imaging
- Computed tomographic imaging
- Electrical imaging
- Fusion imaging
Cardiac Magnetic Resonance Imaging
Cardiac CT
Perfusion Scintigraphy

NC

AC

NC

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NC

AC

Michigan Medicine
Peking University Health Science Center

JOINT INSTITUTE for Translational and Clinical Research
Anti-matter imaging (PET)

Annihilation event between positron & electron

Generates two anti-parallel 590 KeV photons

590 KeV 590 KeV
ELECTRICAL IMAGING OF THE HEART

LA

A

B

Pseudo EG of LA

0 1 2
time (sec)

108 m sec

8
Cardiology: A **device technology revolution**

- **Pump**
  - Mechanical Circulatory Support
    - VADs
    - Total Artificial Heart
    - Stem cell patches

- **Valves**
  - Aortic, Mitral, Tricuspid
  - Chordae tendineae

- **Electric Circuitry**
  - Novel ablation: catheter-based, radiotherapy
  - Leadless Pacemakers
  - Biological Pacemakers

- **Vessels**
  - Angiogenesis
  - New graft biomaterials
Aortic Valve Stenosis
Replacing heart valves without surgery
www.ncbi.nlm.nih.gov/pmc/articles/PMC6288219/
Colli et al.
Implantation of World’s smallest Leadless Pacemaker
Total Artificial Heart
Cardiology: A cellular revolution

- Pump
  - Stem cell patches
- Valves
  - iPS-derived valve in a dish
- Electric Circuitry
  - Biological Pacemakers
- Vessels
  - Angiogenic sprouts
- The Microbes within
Patient-specific induced human pluripotent stem cells (iPSCs) to regenerate cells of the heart

Skin biopsy, blood, amniocytes

Patient specific stem cells (hiPSCs)

Cardiomyocytes

Vascular Cells

Oct4

cvcregenerationcore@gmail.com

Courtesy, Todd Herron
3-Dimensional hiPSC-CM cardiac organoids

A. 3D Microtissue Mold
Top View
Side View

B. 
Relaxed
Contracted

C. 

Courtesy, Todd Herron

Michigan Medicine
Peking University Health Science Center

Joint Institute for Translational and Clinical Research
Human cardiomyocytes “Made In Michigan”

Spontaneously contracting human cardiac monolayer

Courtesy, Todd Herron
Precision diagnosis: iPSC-derived cardiac myocytes

- Rich database of deeply phenotyped patients
- Strategic mechanistic studies that capture genetic and clinical variability of cardiomyopathy
- Patient iPSC-derived cardiomyocyte platform for robust phenotyping and testing

22 yo with TNNT2 mutation, 30 mm septum, ICD shocks, class III heart failure

20 yo brother with TNNT2 mutation, unaffected

Contractile and Structural Quantification
Stress Responses
Pharmacologic Testing

Courtesy, Adam Helms
High Throughput Medication Screening for Cardiac Side Effects
(Rhythm Disturbances)

Cell Line 1
Cell Line 2
Cell Line 3

Courtesy, Todd Herron, Jose Jalife
Drug Induced Torsades de Pointes (TdP) in a dish!

Baseline

+High Risk hERG Blocker
(E-4031)

hERG-specific Blocker

J. Jalife & T. Herron
iPSC-derived cardiomyocytes show phase 4 depolarization \emph{in vitro} ...

... and pacemaker function \emph{in vivo}

Humans as micro biomes:
- 100 trillion microbes in human intestine.
- 3 million genes (100X).
- 2 kg weight.
- 300-1000 species of bacteria.
- control almost all body functions.
Who Are We?

Microbial abundance raises the question: how human are we?

Human:
- 10 trillion human cells
- 20,000 human genes

Microbiota:
- 100 trillion microbial cells
- 20 million microbial genes

99.9% of our genomes the same, but our microbes...?
I HAVE THE RESULTS FROM YOUR STOOL SAMPLE...

DELICIOUS
Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis


Nature Medicine 19, 576–585 (2013) Download Citation ↓

Abstract

Intestinal microbiota metabolism of choline and phosphatidylcholine produces trimethylamine (TMA), which is further metabolized to a proatherogenic species, trimethylamine N-oxide (TMAO). We demonstrate here that metabolism by intestinal microbiota of dietary L-carnitine, a trimethylamine abundant in red meat, also produces TMAO.
Carnitine converted by gut flora to atherogenic TMAO

Hazen Nature Med 2013
Cardiology: An **information revolution**

- Wearables
- Implantables
- Precision diagnosis/treatment
  - Genome
  - Epi-Genome
  - Metabolome
  - Proteome
  - Metagenome
  - Secretome
Continuous Monitoring of ECG

**24 sec**
It helps to rest your arms on a table or your legs.

**HEART RATE**
Your heart has shown signs of an irregular rhythm suggestive of atrial fibrillation.
If you have not been diagnosed with AFib by a physician, you...
Surgical intervention using computerized blood flow simulation

The Engineering that Will Guide Cardiologists

Alberto Figueroa
Computational Modeling of Vascular Hemodynamics through a non-trivial network

Drew Marquis, Pinsky/Beard labs

Michigan Medicine
Peking University Health Science Center

for Translational and Clinical Research
Artificial Intelligence in Cardiology

AI in Cardiovascular Practice

CENTRAL ILLUSTRATION: Role of Artificial Intelligence in Cardiovascular Medicine

- Research and Development
- Clinical Practice
- Population Health

- Novel Therapeutic Agent Discovery
- Precision Disease Stratification
- Integration of Multi-omic Data
- AI-aided Diagnosis
- Therapy Selection
- Optimized Resource Allocation
- Continuous Remote Monitoring and Diagnostics
- Extension of Physician Efficiency and Efficacy

Artificial Intelligence


Michigan Medicine
Peking University Health Science Center

JOINT INSTITUTE for Translational and Clinical Research
The Oracle Red Pill or Blue Pill: We Have a Choice to make

From “The Matrix”
We must choose: we can’t do everything, but we must do something

Consider three cardiovascular focus areas:

(1) Aging of the Cardiovascular system
   – Atherosclerosis
   – Valvular degeneration
   – Diastolic dysfunction/heart failure
   – Atrial fibrillation
We must choose: we can’t do everything, but we must do something:

Consider three cardiovascular focus areas:

(2) Impact of environment

– Internal Environment
  • Microbiome
  • Lipid oxidation
  • BP
  • Other

– External environment
  • Air Pollution
  • Stress
  • Other
We must choose: we can’t do everything, but we must do something

Consider three cardiovascular focus areas:

• (3) Precision diagnosis and treatment
  – Leverage AI
  – Leverage Technology
  – Use of personal stem cells
  – All the ‘omics
To our PKUHSC Friends: Thank you for imagining the future with us. The sky is the limit!