FROM GENES TO HEALTH AND HEALTH TO GENES

1. TRANSLATIONAL – CLINICAL INVESTIGATION

GENES ⇔ CELL ⇔ TISSUE ⇔ PHYSIOL. ⇔ PHENOTYPE ⇔ POPUL. ⇔ HEALTH

TRAINING / MENTORS

ENABLING APPROACHES

Imaging: Non Inv. Molec.
Clinical Proteomics
Inform. / Science / Techn.
Behav. Instrum./ Technol.
Clinical Trials Infrastr.

4. SPECIFIC AIMS

Genetics /Proteomics /Embryogenesis
Regenerative Biol./ Replac. Therapy
Immunobiol./ Inflammation / Thromb
Public Health / Genom. Proteo.

NHLBI SPARK I 1998-2002

NHLBI – Site Visit - March 17, 2006
The “Academician’s Vision”

- The “Clinician’s Vision”

- The “Epidemiologist’s Vision”
CVD & Imaging 2007-2017 - From Treatment To The Understanding & Protection of Health

1. FREEDOM 1
2. VP
3. HRP

From Treatment To The Understanding & Protection of Health

Flow Reversal
Mechanical & Biohumoral Risk Factors

THROMBUS

1) LDL
2) CAMs
3) Extracellular Matrix Fibroblasts
Vasa Vasorum


SMC contract migration proliferation
Potential Origin and Differentiation of Endothelial Progenitor Cells

Embryonic Stem Cell Derived, Cardiovascular Progenitor Cells (FLK Positive Cells)

Adler, ZA Fayad, S Kattman, G Keller et al 2007 (Submitted)
Flow Reversal
Mechanical & Biohumoral
Risk Factors

LDL
CAMs
THROMBUS

1) Extracellular Matrix Fibroblasts Vasa Vasorum
2) SMC contraction, migration, proliferation

Extracellular Matrix Fibroblasts Vasa Vasorum

Vasa Vasorum

Vasa Vasorum and Gadofluorine-Enhanced MR Imaging Science Labor...

Correlation Between 18F FDG-PET/CT And Dynamic Contrast Enhanced MRI Parameters In Human Patients

Neovessels Dysfunction

Morphology

Molecular Determinants
Of Instability
(Hypoxia?)

Intraplaque Hemorrhage
Defense against Intra-Plaque Hemorrhage

Haptoglobin (Hp) Gene*
Two Alleles

Hp-1

Hp-2

Hp-2 is an inferior protein when compared to Hp-1

* Chromosome 16q22

PLAQUE WITH INFLAMMATION & RUPTURED IEL

Moreno PR, Purushothaman K-R, O’Connor WN, Fuster V. Circ. 2002;105:2504
MRI-LIPID LOWERING (SIMVASTATIN 20 or 80 mg/d) AND REGRESSION OF ATHEROSCLEROSIS

Baseline

24 months follow up

C Lima et al., Circ 2004; 110:2336 (Hopkins, Baltimore)
BAD - Multi Slice Black Blood Imaging Rapid Extended Coverage (REX) Turbo Spin Echo Technique

Longitudinal View

Mid heart Aorta- 12 slices

Yonemura A, Momiyama Y, Fayad ZA et al. JACC 2005; 45: 733

Movimama, A Yonemura, ZA Fayad et al 2007 – Up to 2 years

BAD (Fayad ZA, Mani V, Fuster V et al.) 2007 – Predicts CAD
Correlating Change in Vessel Wall Area From Baseline to 1-yr and % Reduction in LDL-C Levels ($\Delta$LDL-C)

Thoracic Aorta

Abdominal Aorta

$r=0.61$

$P<0.001$

$r=0.30$

$P<0.01$
Flow Reversal
Mechanical & Biohumoral
Risk Factors

1) LDL
2) CAMs
3) MMPs

THROMBUS

LDL
CAMs
MMPs
THROMBUS

PDGF

Extracellular Matrix
Fibroblasts
Vasa Vasorum

SMC contracti
migration
proliferation

Fuster V et. al.
PPAR, HDL-C: A New Potential Therapeutic Target for the Prevention of Cardiovascular Disease

3 major pathways by which HDL may mediate cholesterol efflux from the cholesterol-loaded macrophages and 3 major family molecules being involved - PPAR, HDL, CETP

MRI - HDL-Cholesterol

Rabbit / IV HDL, Apo E / HDL, Rabbit / PPAR-y / Fenofibric Acid

High-chol. Diet

Simv. + PPAR

Badimon JJ, Badimon L, Fuster V, JCI 1990; 85:1234 - Apo A1 in Rabbits

JX et al Circ 2001;104:244;


Jensen SE JAMA 2003;290:2292 - Apo A1 in Humans - IVUS
8) FREEDOM, Asian, 64 yrs, DM2, ex-smoker
BAD, CT - FDG Uptake Aortic Arch

HF Rudd, ME Farkouh, V Fuster, ZA Fayad, JACC 2007;50:89
Detection of Macrophages in Aortic Atherosclerosis of Hypercholesterolemic Rabbits with 64-Slice CT. Novel Contrast Agent N1177

Before injection  
During injection  
2 hours after N1177


Fused MPR of angiography and hour acquisition

Transmission EM  
Absorption spectrum on Scanning EM
CVD & Imaging 2007-2017 - From Treatment To The Understanding & Protection of Health

- VP
- HRP
- HEALTH

1. FREEDOM 1
2. FREEDOM 2
3. FREEDOM 3

FUTURE REVASCULARIZATION EVALUATION IN PATIENTS WITH DIABETES MELLITUS: OPTIMAL MANAGEMENT OF MULTIVESSEL DISEASE

- EPC Markers
- Statins: Crestor 20
- Niacin 2000 IR,

Risk Factor Profile,
BAD / MRI – AoCo / MRI - CT / PET
Clinical Events

- V Fuster (2005-2010)
FREEDOM -3

Type 2 Diabetes Mellitus Patients with Multi-Vessel CA

1. Plaque Imaging: Burden, Characteristics, Vulnerability
   - MRI: Carotid, Aorta, Coronary
   - PET-CT: Carotid, Aorta, Coronary

2. Aggressive: Risk Factor Modification

3. Repeat Plaque Imaging: 18 Months and 3 Years
   Death / Non-Fatal MI / Non-Fatal Stroke / Revascularization: 3 Years

4. Correlation: Plaque Burden / Characteristics / Vulnerability
   With: Clinical Events and Risk Factor Burden

Integrated Plaque Score: To Predict Clinical Events
The “Academician’s Vision”

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CVD & Imaging 2007-2017 - From Treatment To The Understanding & Protection of Health

HEALTH

2 VP

3 HRP

1

FREEDOM 1
FREEDOM 2
FREEDOM 3

Atherothrombotic disease
Cardiovascular events

**RISK FACTORS, GENETIC MARKERS, SERUM MARKERS, BIOIMAGING**

- Major risk factors
- Genetic Markers
- Serum Markers
- Imaging Markers

Sanz, V Fuster, JF Viles-Gonzalez, P Moreno 2007 (In Press)
Imaging Data Handling: Overview

Scan subjects on mobile units

Upload to secure eRoom

Images retrieved by Sinai core imaging lab

QuickTime™ and a TIFF (LZW) decompressor are needed to see this picture.

QuickTime™ and a TIFF (Uncompressed) decompressor are needed to see this picture.

3T MR

PET/CT
Randomization - Imaging vs Framingham Only

- Imaging N=6000
  - Imaging Risk CT, US, AAA, ABI
    - Imaging Risk High (regardless FRS)
      - CE-CTA or CE MRI (Carotid, Coronary) N=1000
      - No CE MRI (Carotid, Aortic, Coronary) N=1000
    - Imaging Risk Not High
      - PET-CT N=200

- No Imaging Framingham N=1300

Event Monitoring 3 Years
Blood sampling
5) CT- Angio

6) MRA

Fuster V, Kim RJ, Circ **2005;112:135**
Robin Roberts – Good Morning America – Jan 31, **2006**
7) To Quantify Coronary Plaque Burden (CPB)

Asian, 64 yrs, DM2, ex-smoker
BAD, CT- FDG uptake ascending aorta

In 26 Pts. Inflammation: Inverse Colocalization with CCS
Colocalized with Lipid Rich Areas
More Predominant in Diabetics

HF Rudd, ME Farkouh, V Fuster, ZA Fayad, JACC 2007;50:892
Tahara et al JACC 2006; 48:1825 (Kurome) - Simvastatin
DES
Large lipid core
Posit. Remodelling
Focal, proximal lesion
One non-flow limiting lesion
Invasive assessment
Posit. non-invasive imaging
Identify high-risk patients (Framingham)

Systemic therapy

Benefit ???
Cost ???
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CVD & Imaging 2007-2017 - From Treatment To The Understanding & Protection of Health

1. FREEDOM 1
2. FREEDOM 2
3. FREEDOM 3

VP
HRP
HEALTH

1) CHILDREN: MODULATE BEHAVIOR

Young children (3-10 years):
Plaza Sésamo Colombia,

Youth leadership through the Colombia enterprise:
Global Youth Meeting for Health, Delhi, November 2007
Cahan, ED. Science 2007;316:835.

The child as a scientific object
EUROACTION
8 countries 24 centres
8657 subjects
2) WHF – The Grenada Heart Project

1975  2000
• High prevalence of hypertension
  - 23% by self report
  - 28% > 140/90 mm Hg

• High prevalence of diabetes
  - 9.8% by self report
  - 8.5% > 126 mg/dl glucose
ADULTS DON’T CHANGE
4a) New Perspective on Nonprescription Statins: An Opportunity for Patient Education and Involvement

Valentin Fuster, Am. J. Card 2007; 100: 907
4b) POLYPILL

CORONARY DISEASE & CORONARY EQUIVALENTS

- ASA
- STATIN
- ACE INHIBITOR
- BEHAVIOR MODIFICATION

ECONOMIC, SIMPLE (ADHERENCE)

4b) Preliminary schedule

- **2006**
  - Project Definition
  - Participant Selection
  - Project Organization

- **2007**
  - Regulatory consultation
  - Project Approval
  - Combination selection
  - Preclinical Studies

- **2008**
  - Formula Selection
  - Bio-equivalence
  - Patents
  - Development of Training Plan / (Treatment Guidelines)

- **2009**
  - Dossier Evaluation
  - Clinical Results

- **2010**
  - Dossier Approval
  - Registration
  - Launch

*V Fuster, G Sanz, Nature Cardiov Med. 2007;4:17*
5) Why have a package?
TO ADDRESS NCD BY PHC
IO/ISH-Modified simple variables 2007 (3 vs >3)

Blood pressure
"belt" Perimeter
Cholesterol
Blood sugar (2)
Smoking
Physical Activity
Age

<table>
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<th>Age</th>
<th>Male</th>
<th>Female</th>
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<td>Smoker</td>
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Immunobiol./ Inflammation / Thromb.
Public Health / Genom.Proteo.

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NHLBI – Site Visit - March 17,2006
Training / Mentors

**CVMR-ISL**
- SH Aguiar MD
- S Amaerbiaken MD
- C Calcagno MD
- JC Cornily MD
- Zahi Fayad, PhD
- Fabien Hyafil PhD
- Vitalii Itskovich, PhD+
- Michael J Lipinski
- V Mani M
- James HF Rudd MD
- Javier Sanz, MD
- Mark Sirol, MD
- E Vucic MD

**Cardiology**
- Valentin Fuster, MD, PhD
- Juan J Badimon, PhD
- Michael Poon, MD
- Stella Palentia, RN
- Don Smith, MD
- Pedro R Moreno MD
- Michael E Farkouh

**Molecular Biology**
- Edward Fisher, MD, PhD
- AP Levy MD
- Ernane Reis, MD

**CV Research Fellows**
- Sameer Bansilal
- Roberto Corti, MD
- Juan F Viles MD
- Randolph Hutter MD
- Borja Ibanez MD
- Claudia Calcagno PhD

**Neurology**
- Jessey Weinberger, MD

**Pathology**
- John Fallon, MD, PhD
- KR Purushothaman, MD

**Funding**
- NIH-HL 94013
- NIH-HL 61801
- NIH-HL 07208