Department of Medicine
Li Ka Shing Faculty of Medicine, HKU

HKU Develops Chimeric Mouse Liver Model Helps Familial Hypercholesterolemia Patients Test Drug Response

Press Conference
April 20, 2017

Speaker

Professor Tse Hung-fat

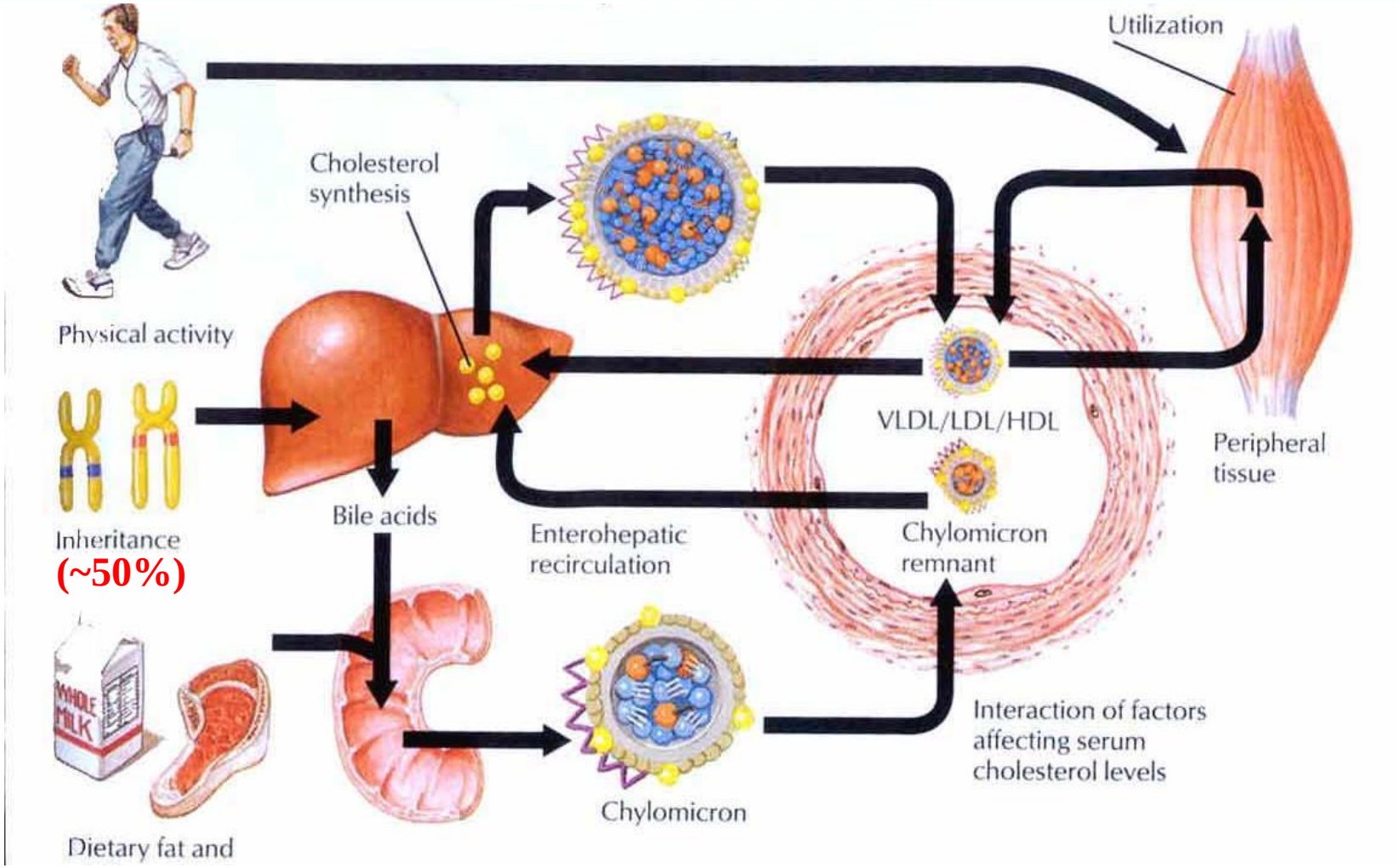
William M W Mong Professor in Cardiology

Chair Professor of Cardiovascular Medicine

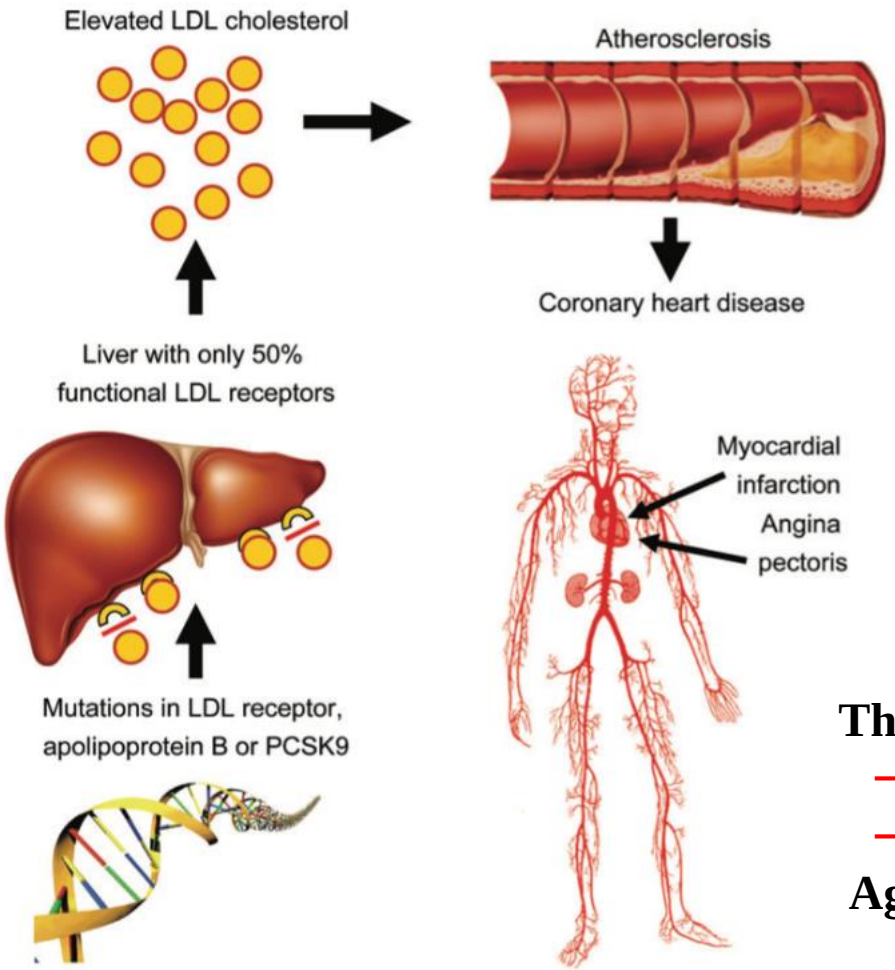
Department of Medicine

Li Ka Shing Faculty of Medicine, HKU

Hypercholesterolemia

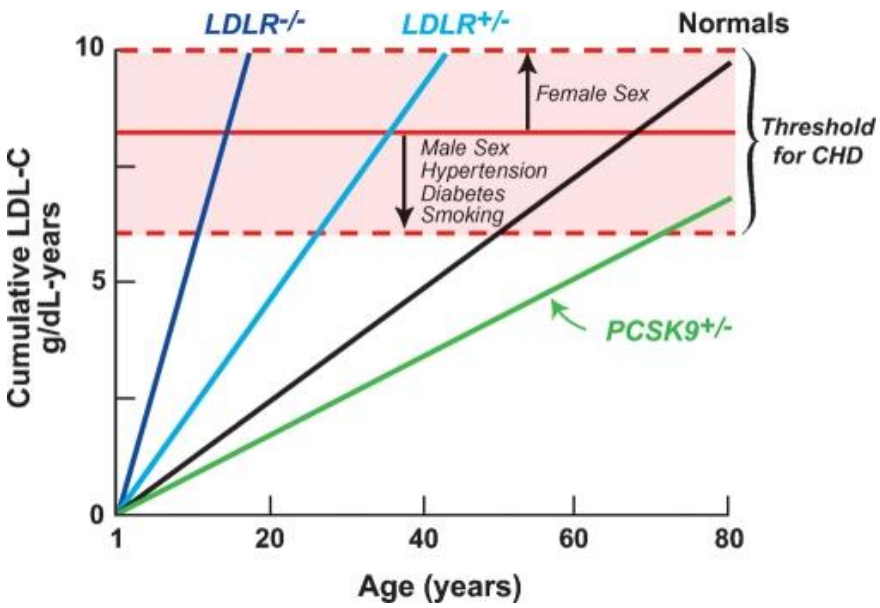


Familial Hypercholesterolemia



European Heart Journal, 2013

Age Patients Meet CHD Threshold



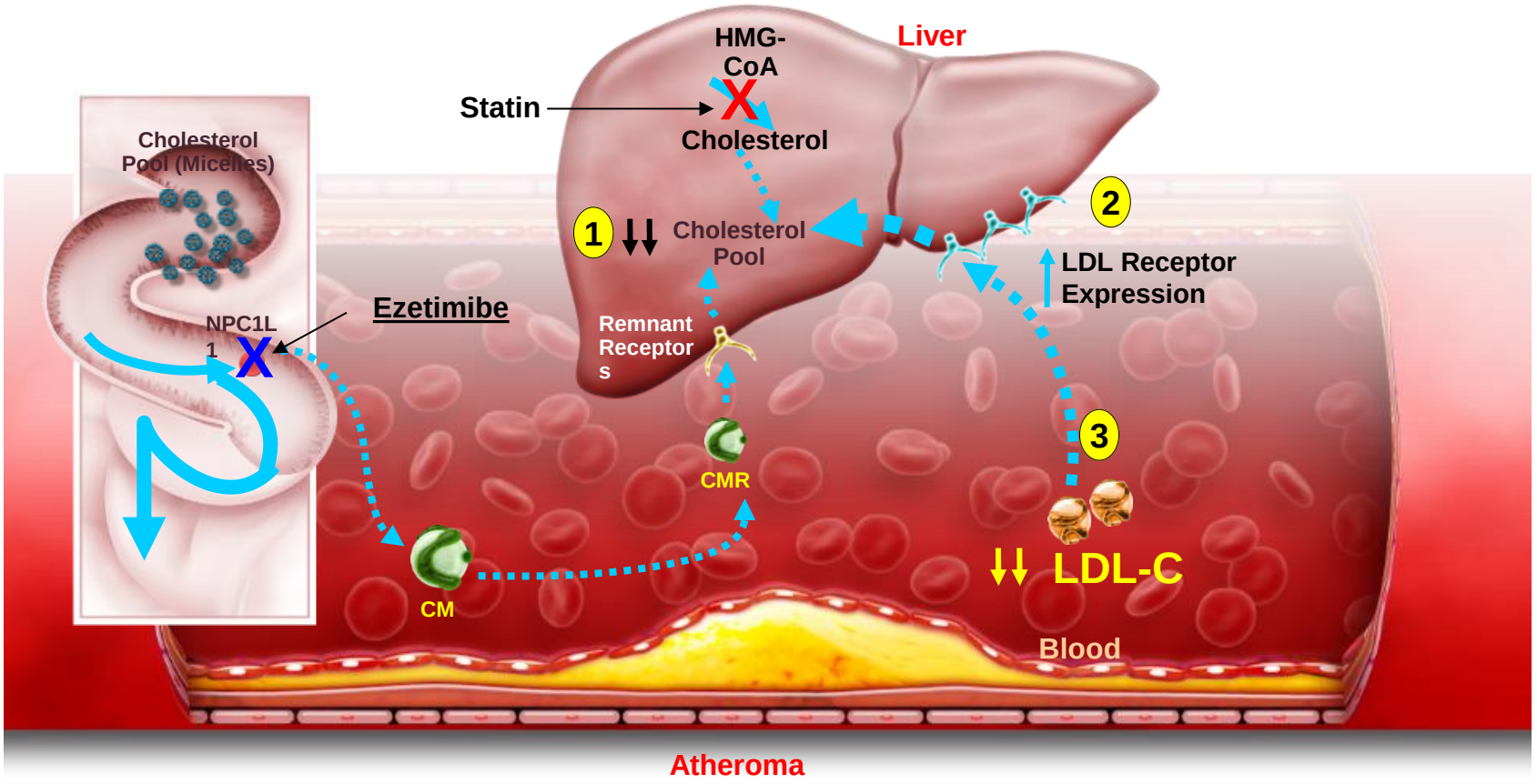
Threshold for CHD reached by :

- **Age 15 y in HoFH patients (1 in million)**
- **Age 40 y in HeFH patients (1 in 200-500)**

Age > 60 y in healthy individuals

Horton JD, et al. J Lipid Res. 2009

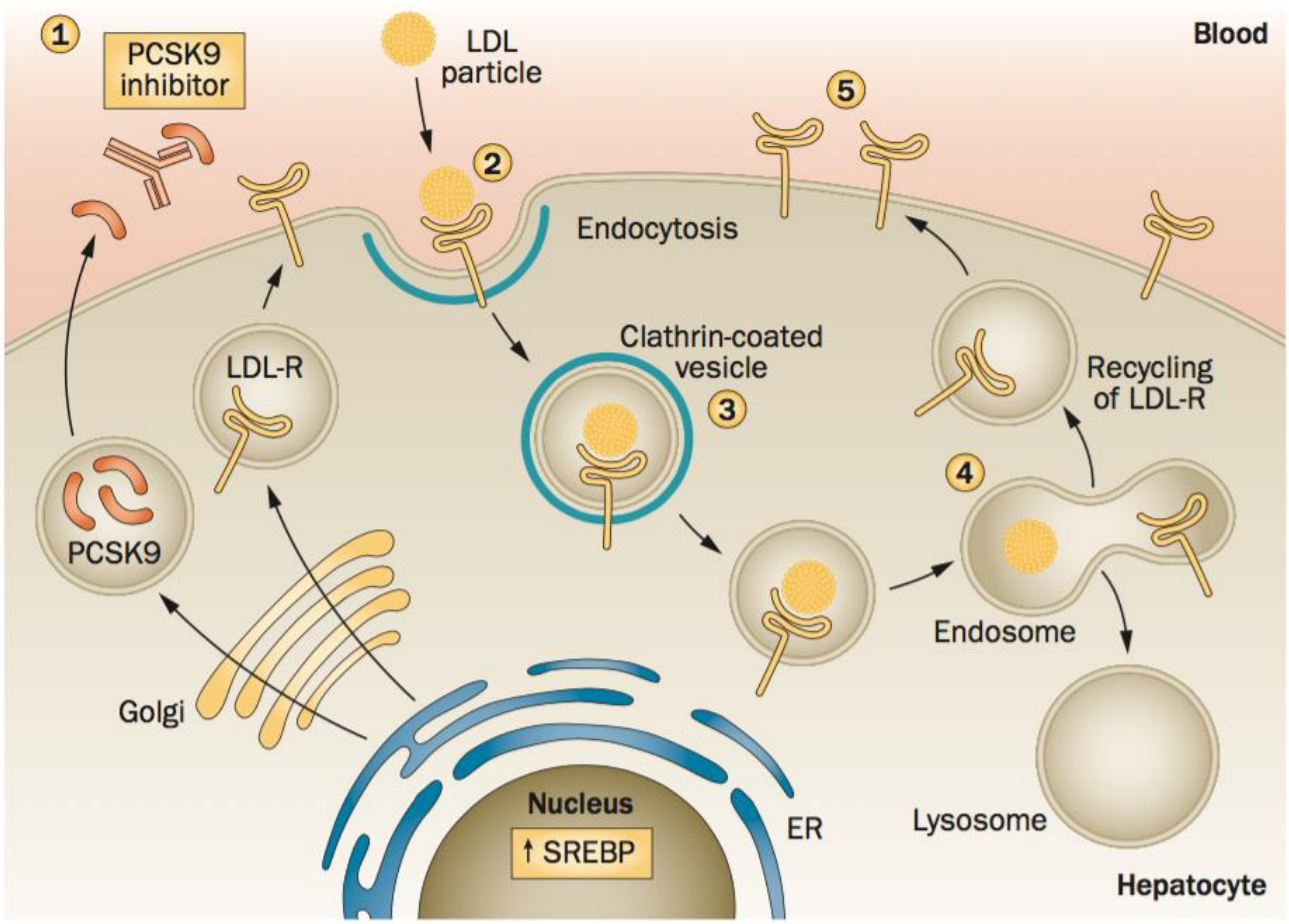
Treatment of Hypercholesterolemia



NPC1L1 = Niemann-Pick C1-like 1; HMG-CoA = 3-hydroxy-3-methylglutaryl acetyl coenzyme A; CMR = chylomicron remnant.

1. Grigore L et al. *Vas Health Risk Manag*. 2008;4:267–278.

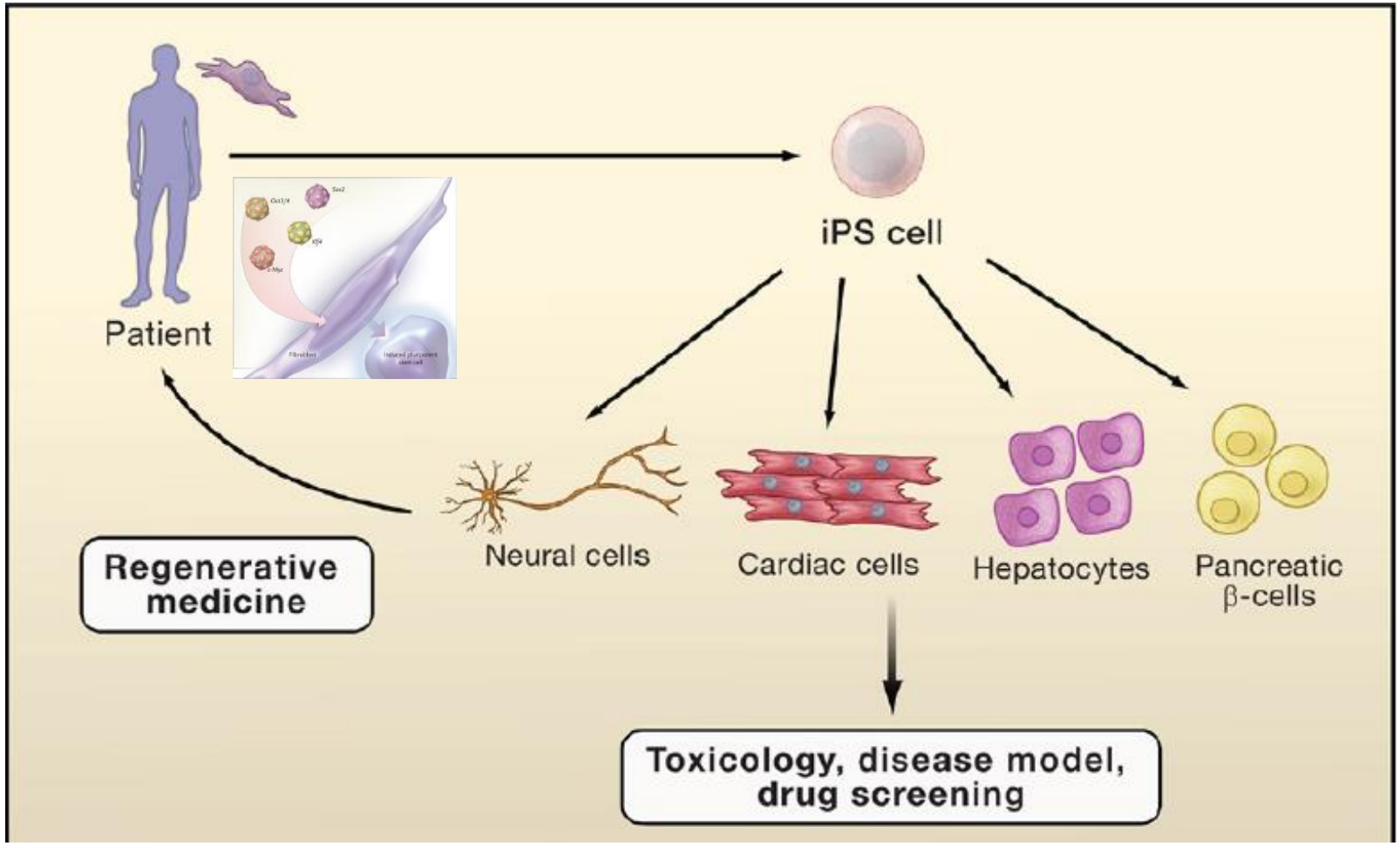
New Biological Therapy for Hyperlipidemia: Targeting PCSK9 Therapy



Recently approved by FDA

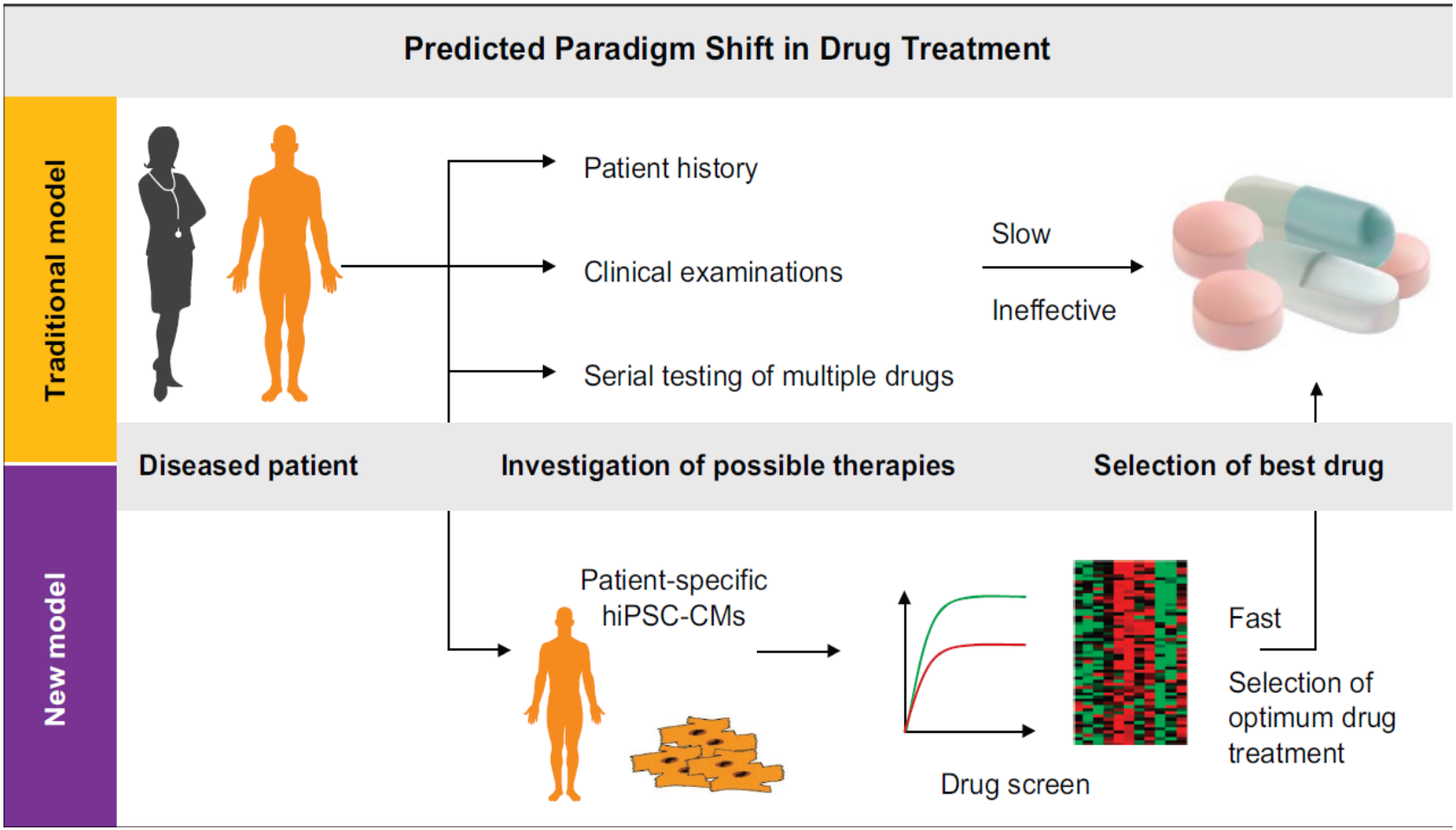
Nature Reviews Cardiology, 2015

Promises of Induced Pluripotent Stem Cells (iPSCs)



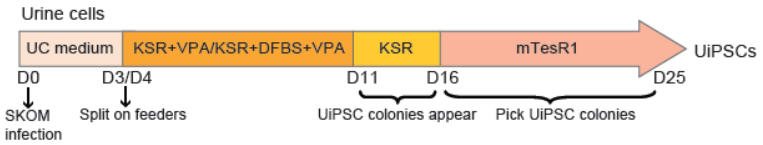
Yamanaka S. Cell 2009

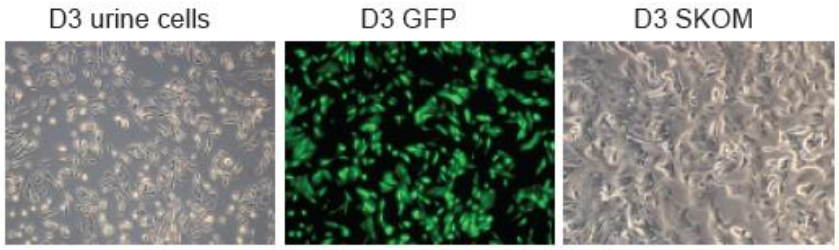
Human iPSC for Drug Screening

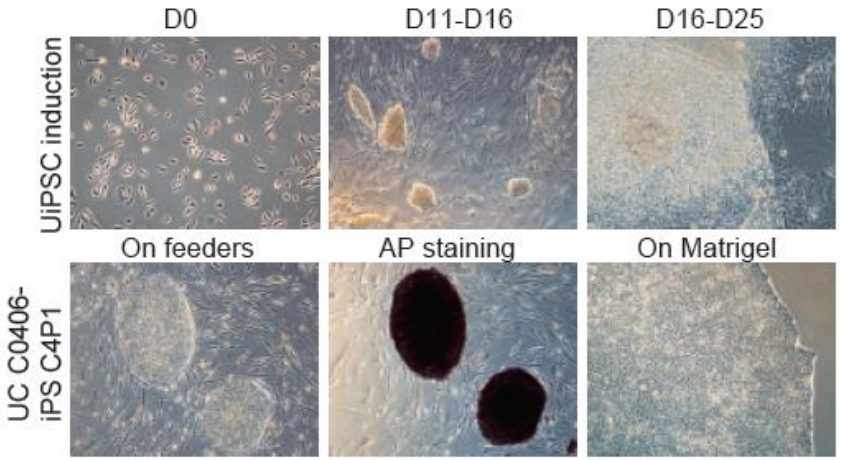


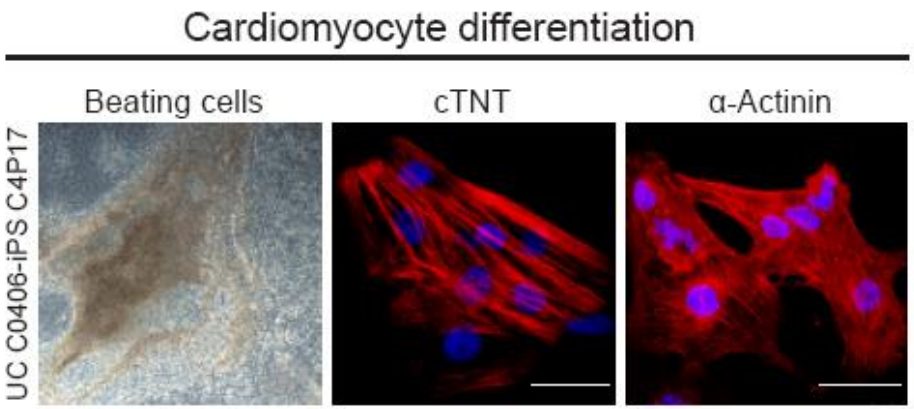
Matsa E, et al. Physiol Rev. 2016 Jul;96(3):1093-126.

iPSC From Urine



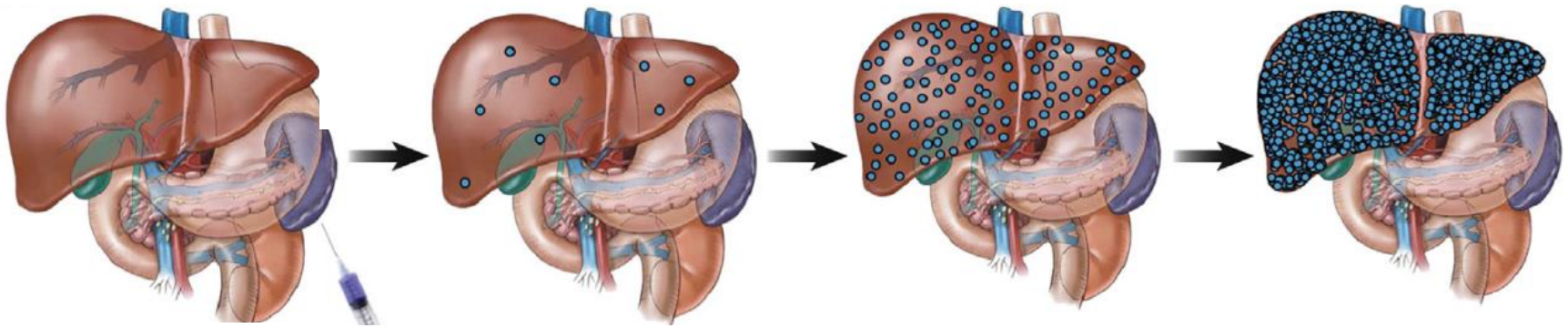






Zhou T, …Tse HF, Estaban MA, et al. Nature Protocol 2012

Human Liver Chimeric Model

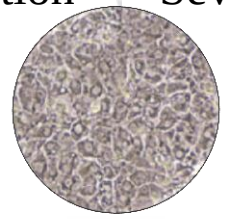


Intrasplenic Injection

Severe liver injury

Human hepatocytes proliferation

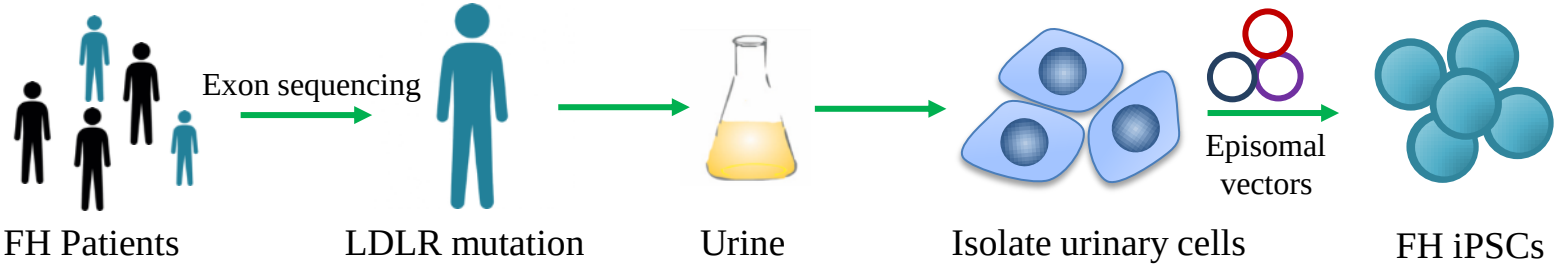
Humanised liver



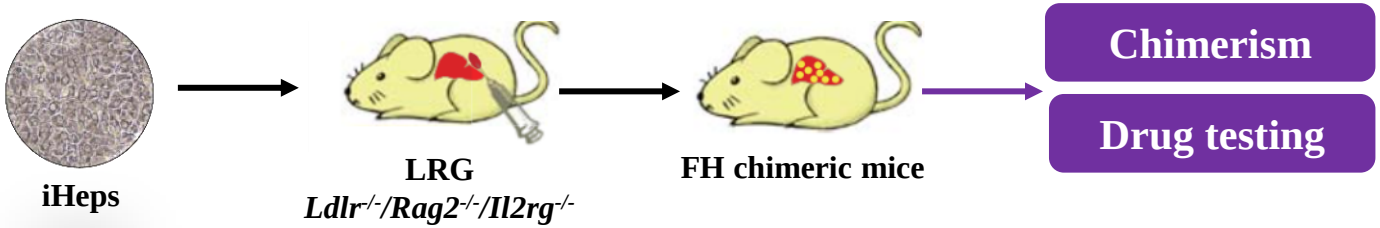
Human Hepatocytes

Grompe & Strom, Gastroenterology 2013

Aims of Study



Directed differentiation

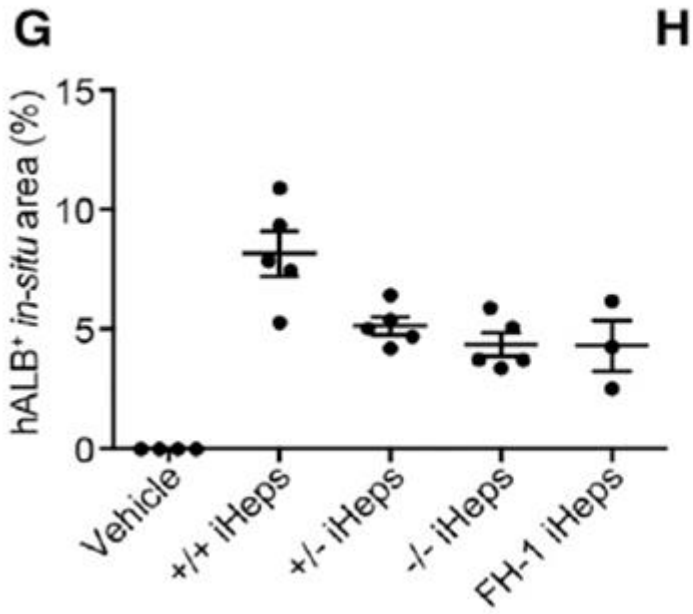


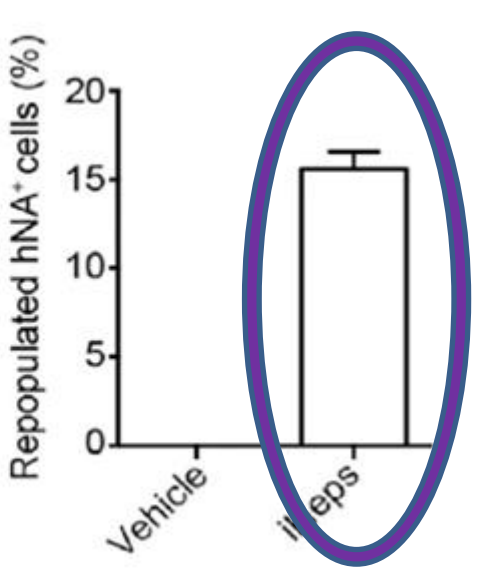
Generation of FH iPSCs and iHeps

Create of chimeric mice

Drug testing

Create Chimeric Mice Engrafted with FH iHeps

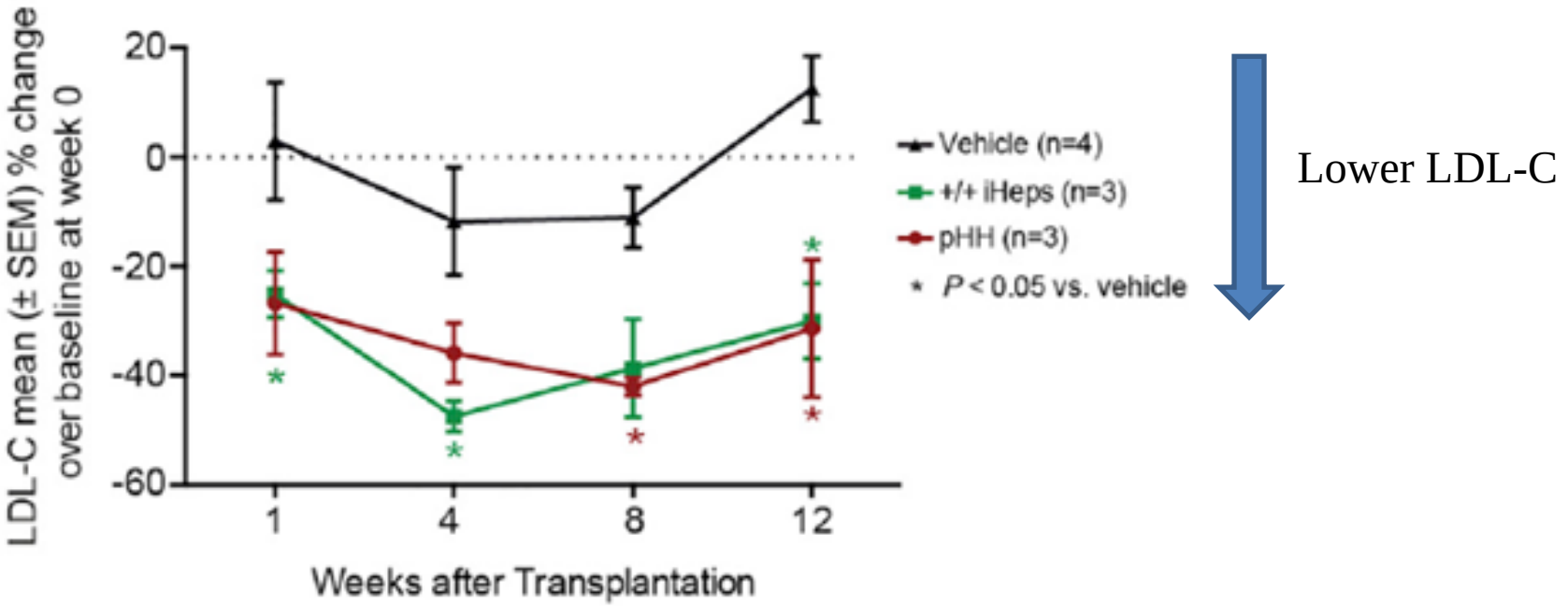




FH chimeric mice

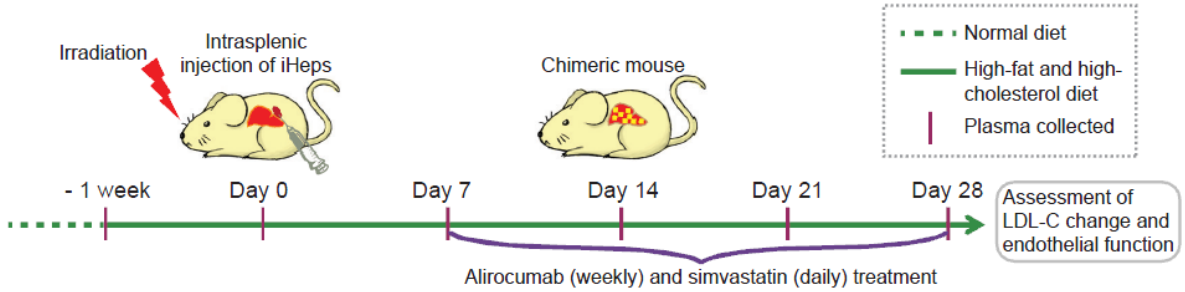
- **Proofs of the repopulation of iHeps in mouse liver**
- **About 15% of human iHeps is engrafted to mouse liver**

Engrafted Healthy iHeps Lower LDL-C in Mice with FH (LDLR-/-)

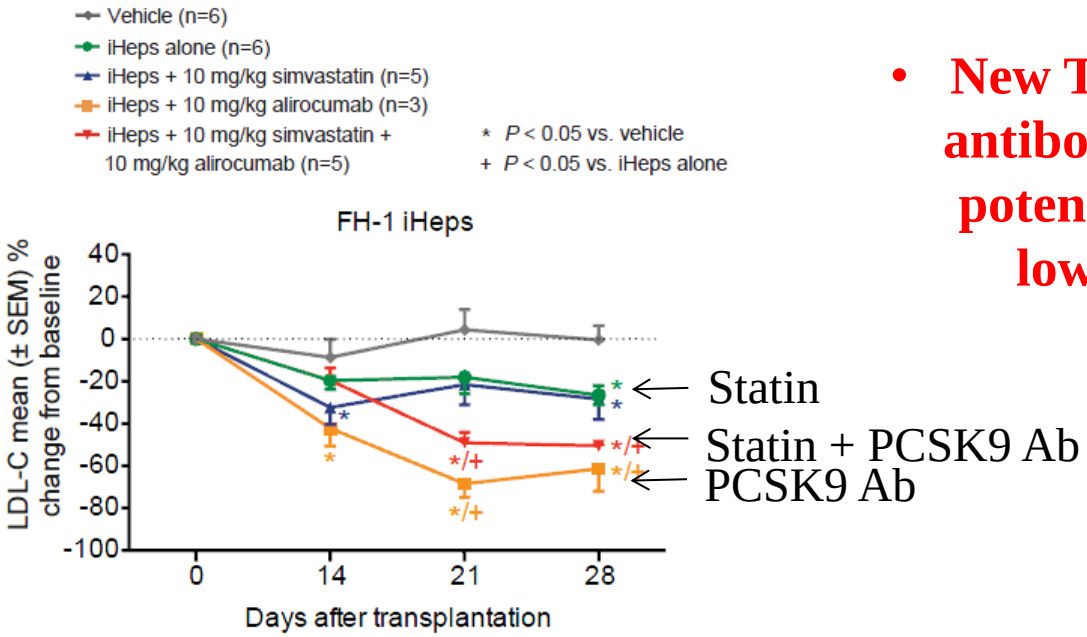


- ✓ **Long-term effects of engrafted iHeps in LDLR null mice**
- ✓ **Engrafted iHeps lower LDL-C in LDLR null mice**

PCSK9 Antibodies: High Potency in Lowering LDL-C

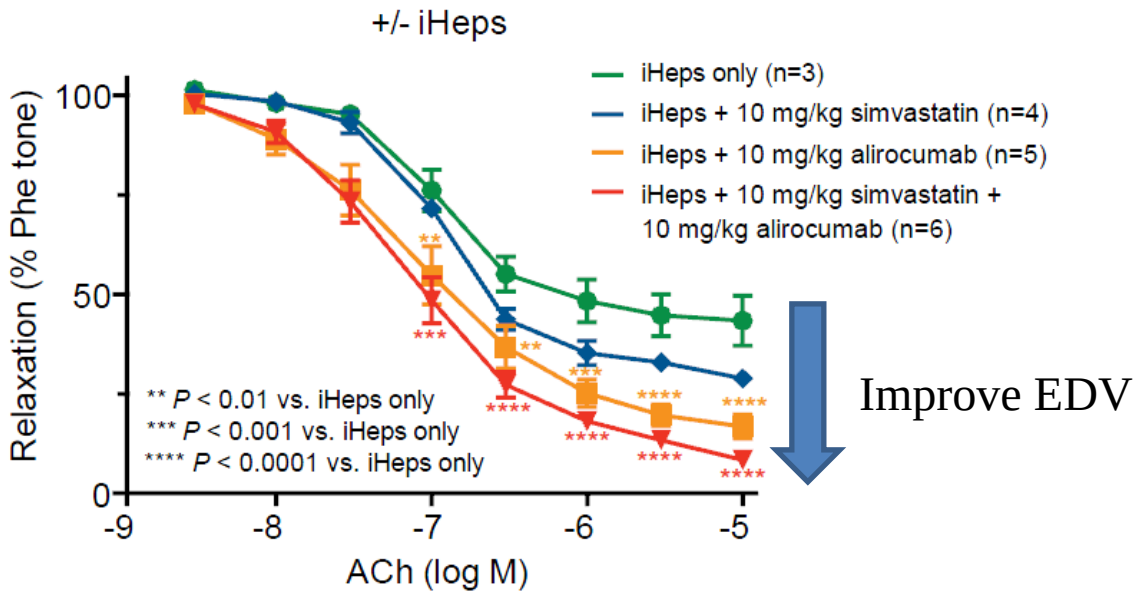


Strategy for in vivo drug testing using LRG mice engrafted with FH iHeps.



- **New Therapy: PCSK9 antibodies show higher potency than statin in lowering LDL-C**

PCSK9 Ab & Statin Improve Vascular Function in Chimeric Mice



- **One consequence of FH is the accelerated development of atherosclerosis on the arterial wall**

- **PCSK9 Ab & Statin improve vascular relaxation**

Summary and Significance

- **Generation of a comprehensive in-vitro and in-vivo stem cell model for drug testing in familial hypercholesterolemia**

- **Generation chimeric mice with engrafted human iPSC-derived iHeps for:**
  - Pre-clinical testing of novel drug therapies targeted on the liver eg lipid lowering agents → Anti-viral agent
  - Disease modeling of inherited liver diseases + drug screening → Wilson disease
  - Future for liver regeneration
  - Development of long-term chimeric model in rabbit

Acknowledgement

Research Grants:

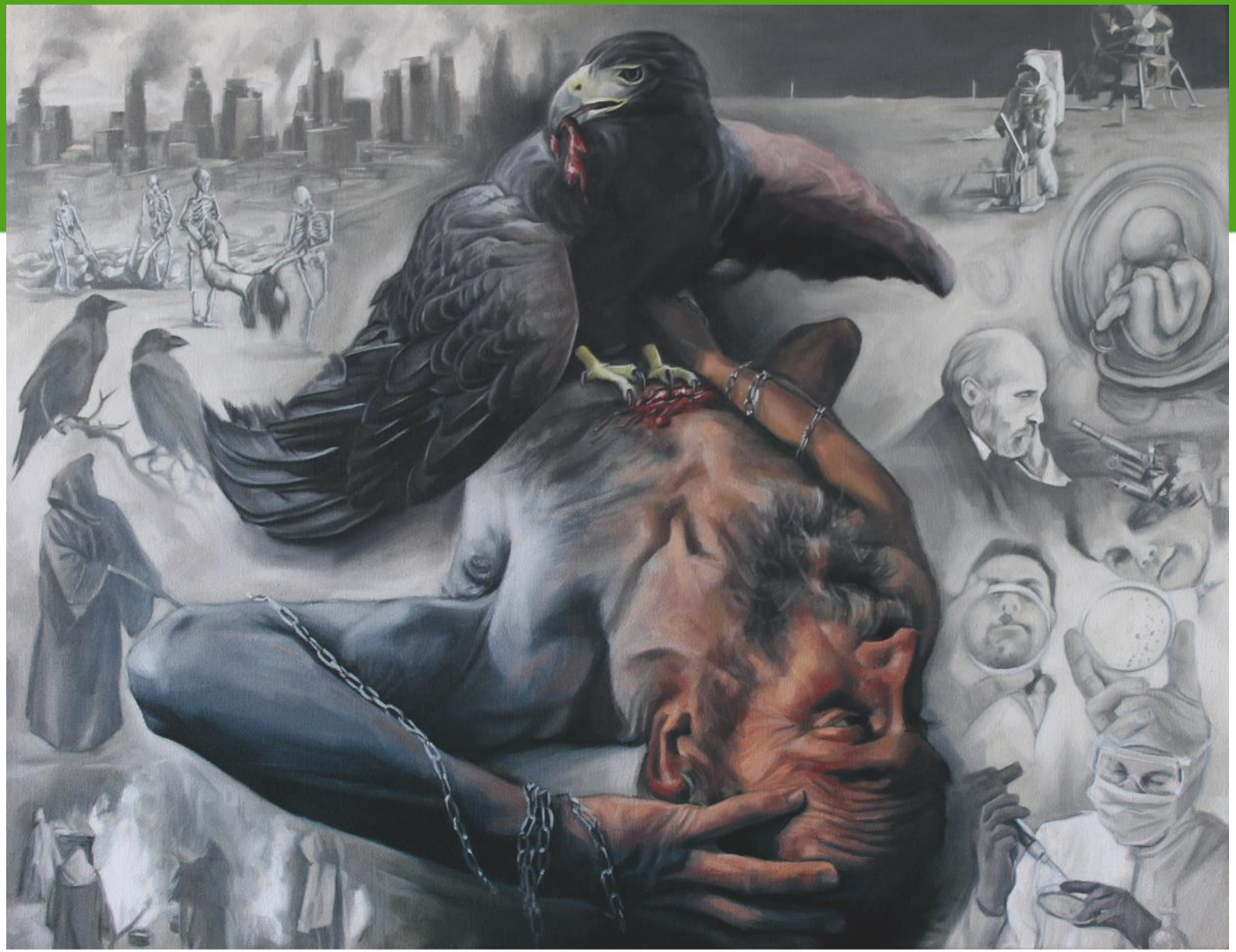
- **Theme-based Research Scheme (TRS):** From Genomic Testing and Biomarkers to Human Pluripotent Stem Cell Platform (T12-705/11)
- **Innovation and Technology Fund (ITF):** Viral-Vector Integration-Free Human Induced Pluripotent Stem Cells Platform Derived from Urine Samples for Disease Diagnosis and Drug Screening (Ref: ITS/303/12)

Donations:

- **Sun Chieh Yeh Heart Foundation**
- **Wong Chak Chui Stem Cell Research Fund**

Collaborator:

Dr Miguel A. Esteban, Guangzhou Institutes of Biomedicine and Health, Chinese Academy of Sciences



Prometheus challenged Zeus by protecting mankind, whom he created according to the Greek mythology, and as punishment he now lies eternally chained to a mountain where his liver is eaten daily by an eagle. Around him humanity has developed, always debating between destruction and progress. In the bottom right corner scientists prepare stem cell-derived hepatocytes to regenerate Prometheus liver. *Design by Nacho Puerto, Miguel A. Esteban, Hung-Fat Tse, and Jiayin Yang.*

Patient's Sharing

Q & A Session