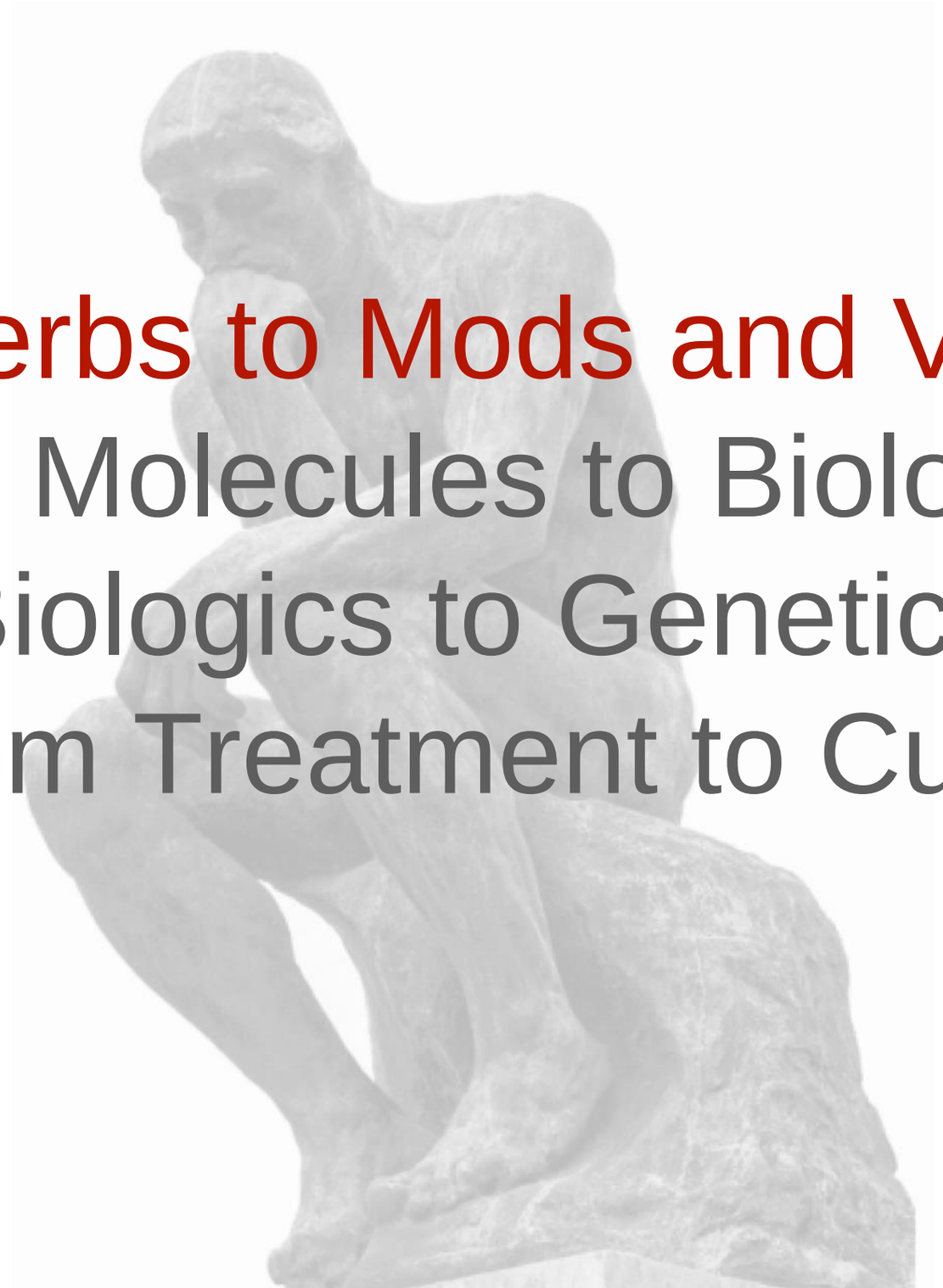
From Herbs to pills, antibodies and nucleic acids: The rise of pharmacotherapy

Professor Thomas F. Lüscher, MD, FRCP
Professor of Cardiology, Imperial College and Director of Research, Education & Development, Consultant Cardiologists, Royal Brompton and Harefield Hospitals, London, U.K. and Center for Molecular Cardiology, University of Zurich, Schwitzerland
www.tomluescher.ch

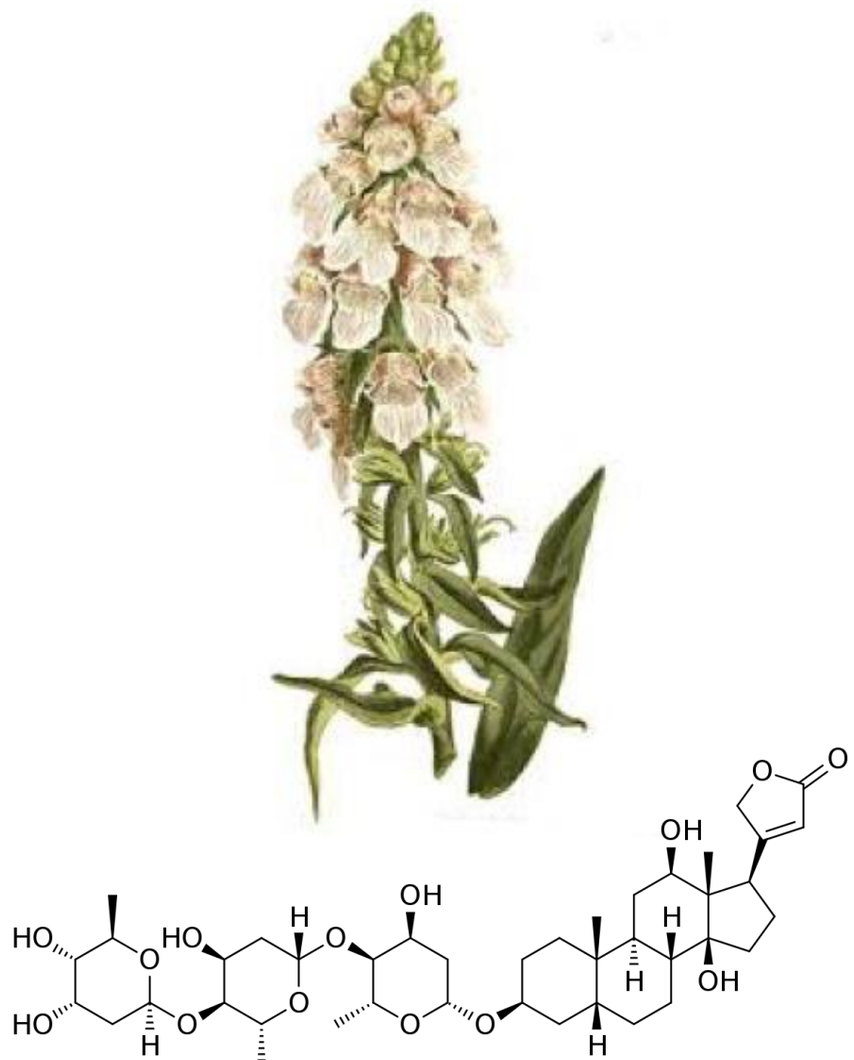
No conflicts of interest related to this topic

Universität Zürich[UZH]
Imperial College London



From Herbs to Mods and Venoms
From Molecules to Biologics
From Biologics to Genetic Tools
From Treatment to Cure

Learning from Nature:
The herbalist „*Mother Hutton*“ and Foxglove

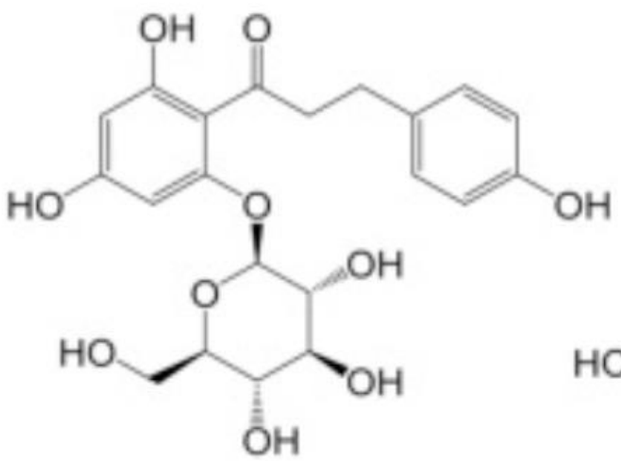


1930, Sydney Smith of Burroughs Wellcome

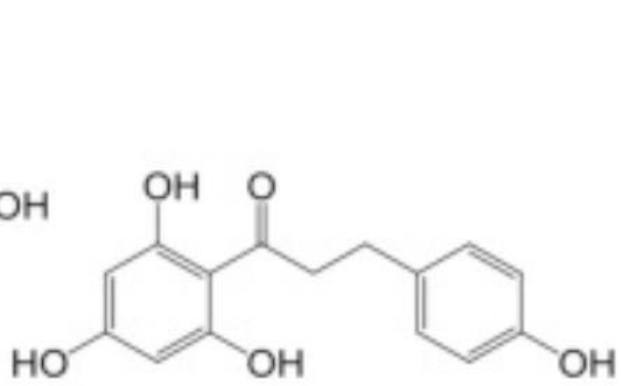
Mother Hutton and William Withering in 1784

The Apple Tree and Sodium-Glucose-Transport-Inhibitors

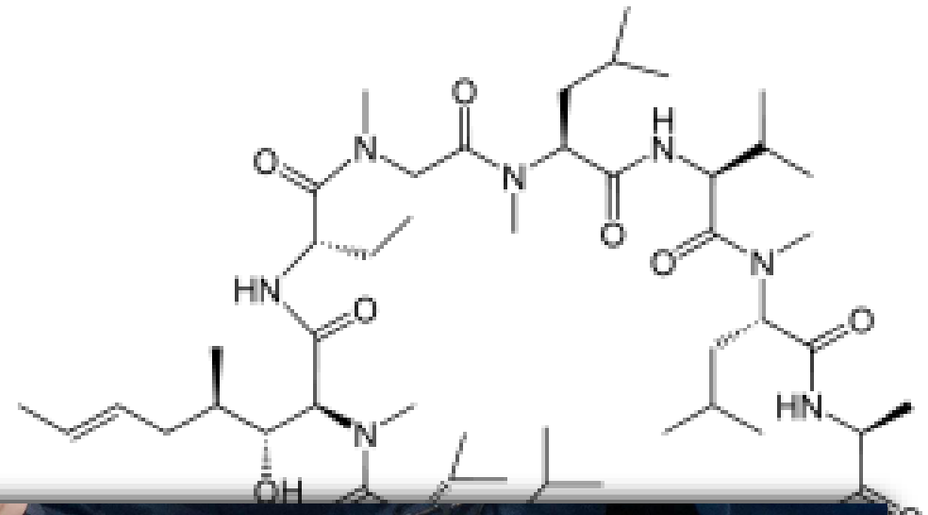
Phlorizin, isolated originally from the **bark of apple trees** in 1835, Joseph Vas Mering describes its pharmacological effects in 1886

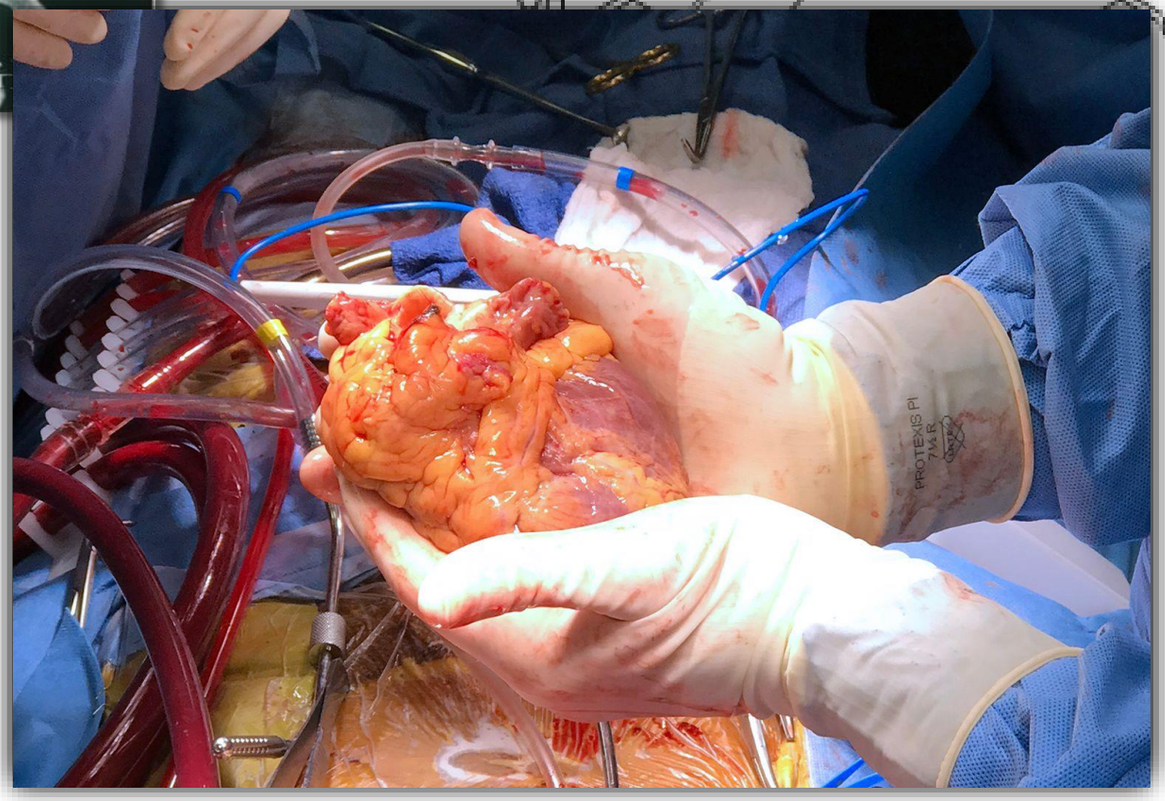


Phlorizin
SGLT2 IC_{50} 21 nM
SGLT1 IC_{50} 290 nM

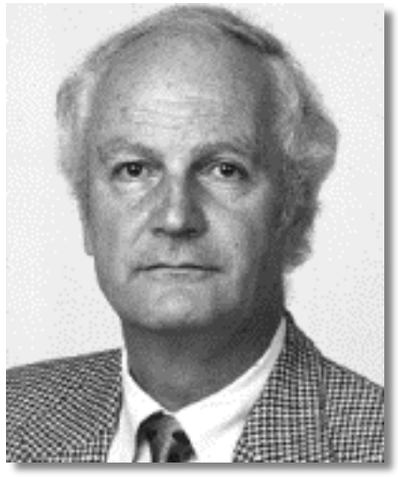


Phloretin
SGLT2 IC_{50} 25000 nM
SGLT1 IC_{50} 50000 nM
GLUT IC_{50}~400 nM

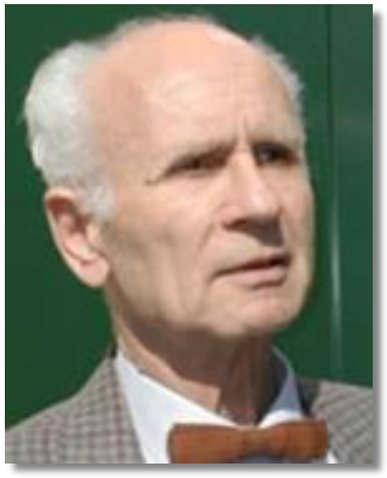




Tolypocladium inflatum

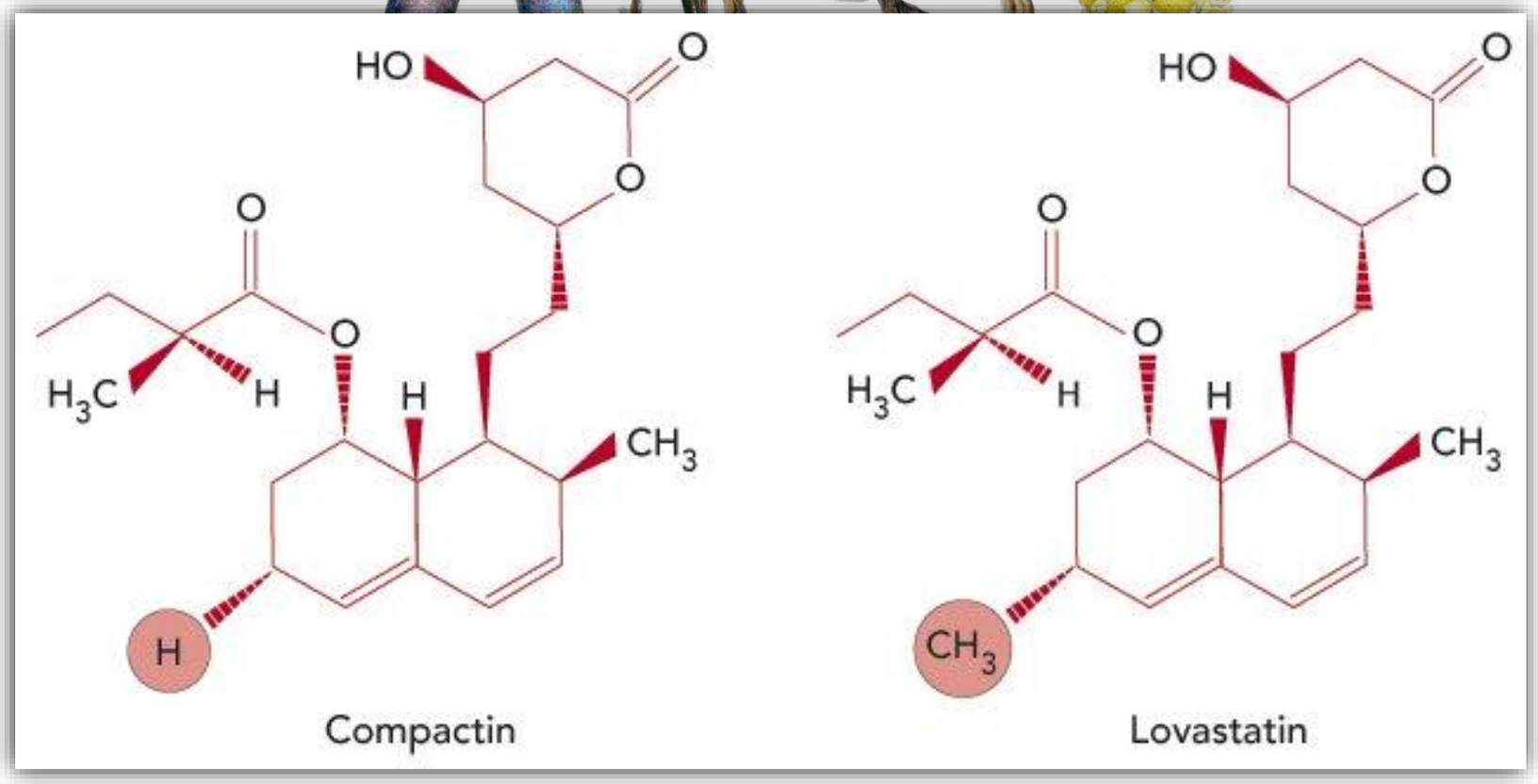


Jean-François Borel

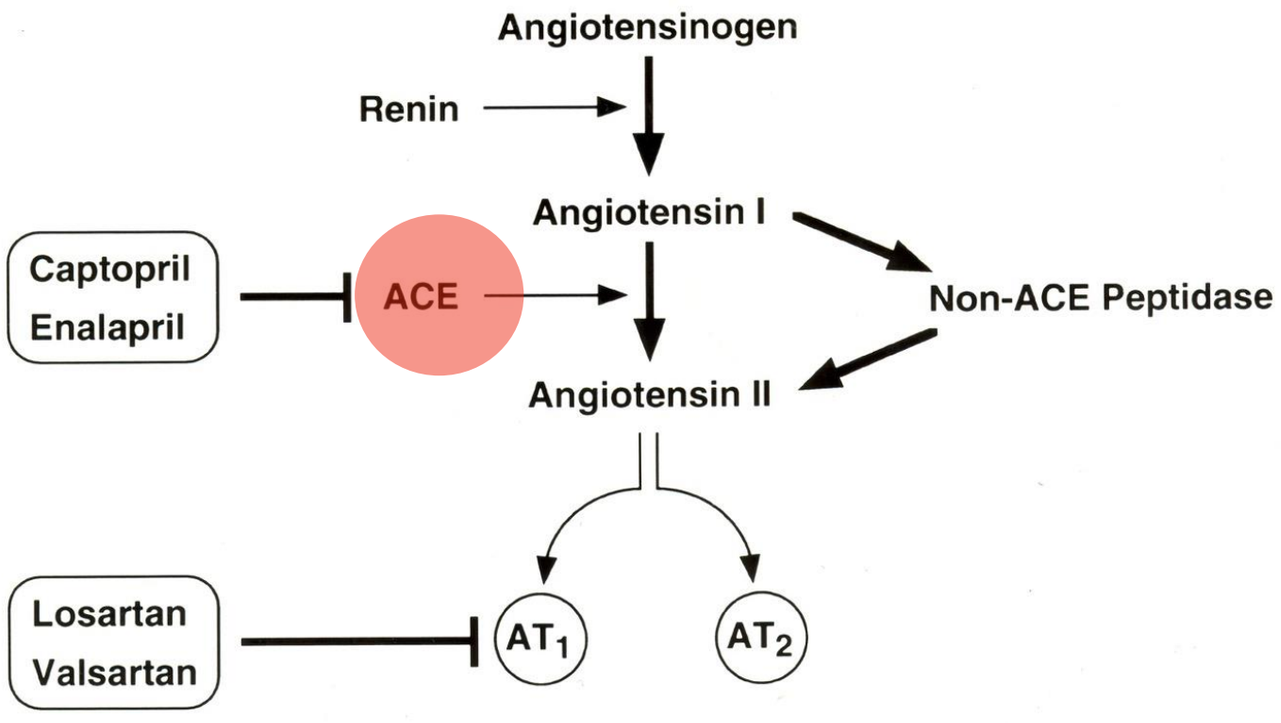


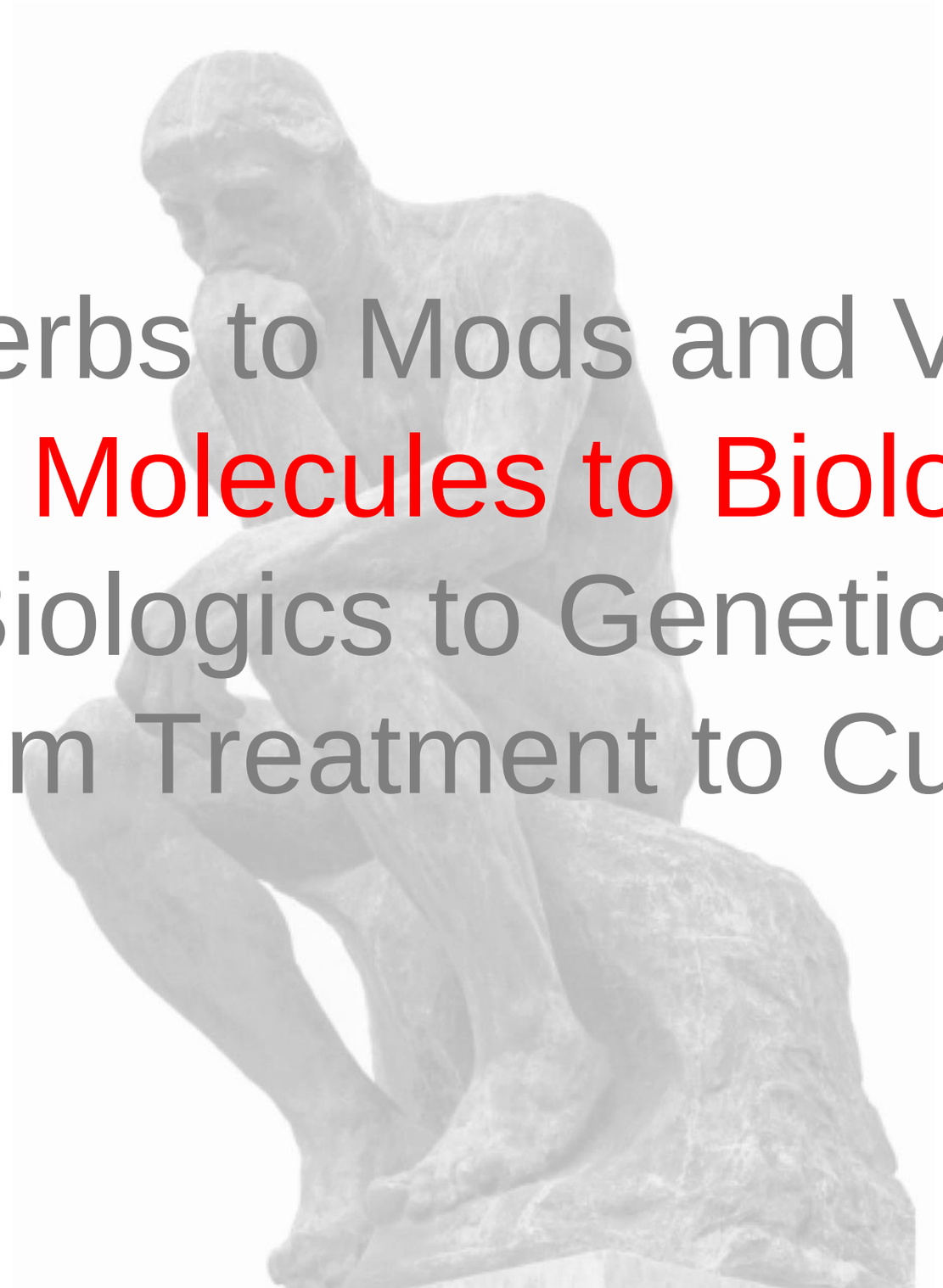
Hartmann Stähelin

I speculated that fungi like molds and mushrooms would produce antibiotics that inhibited HMG-CoA reductase.



Snakes - the Pharmacist of Evolution





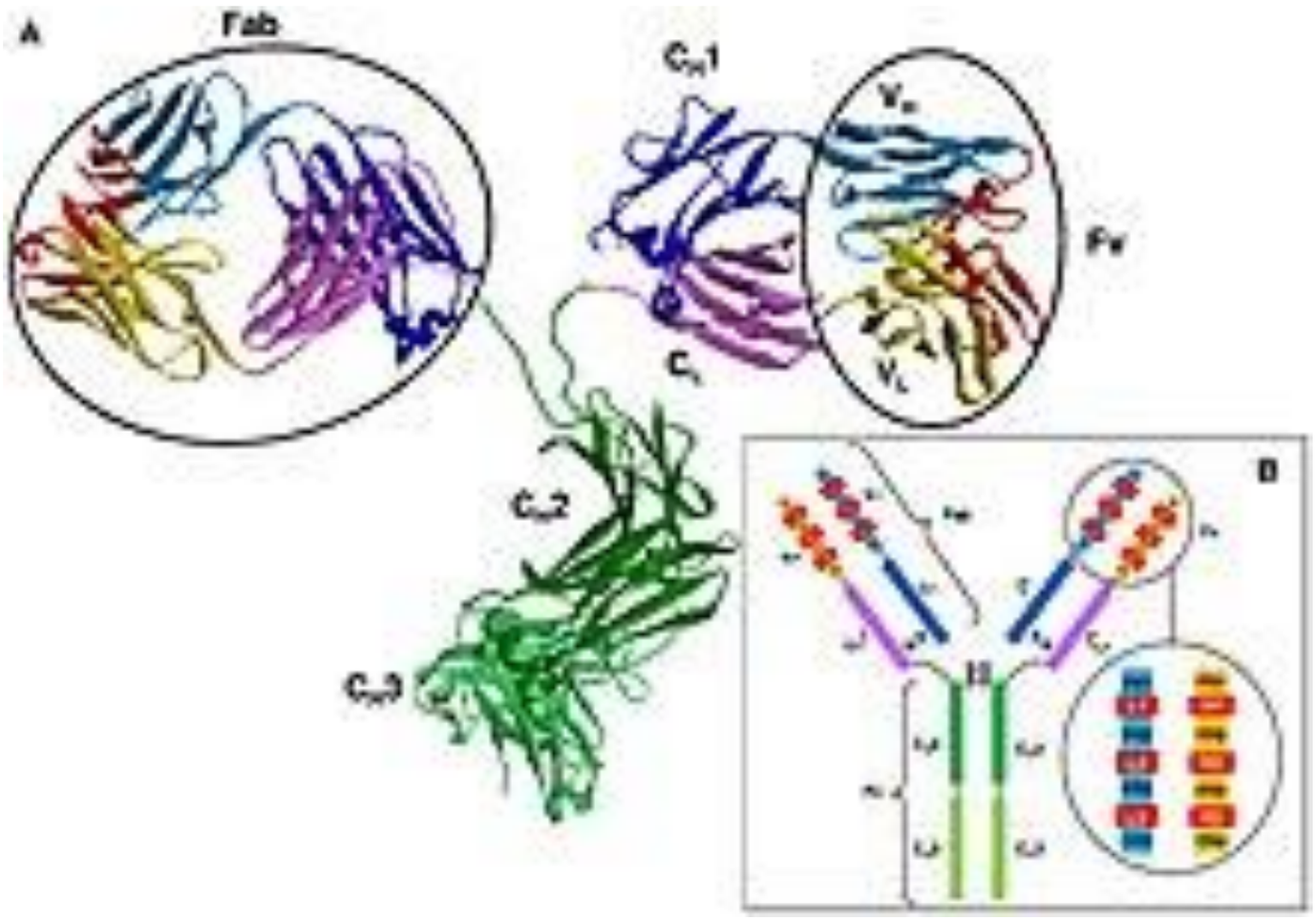
From Herbs to Mods and Venoms

From Molecules to Biologics

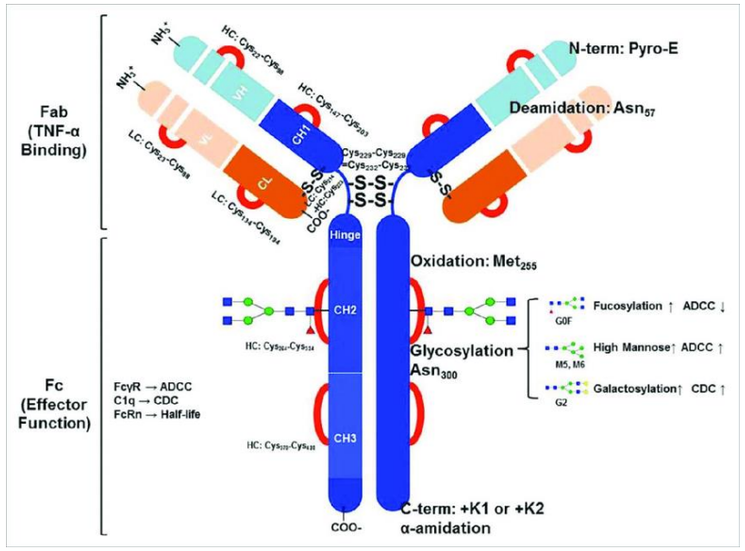
From Biologics to Genetic Tools

From Treatment to Cure

Learning from Nature:
Taking Advantage of the Immunsystem

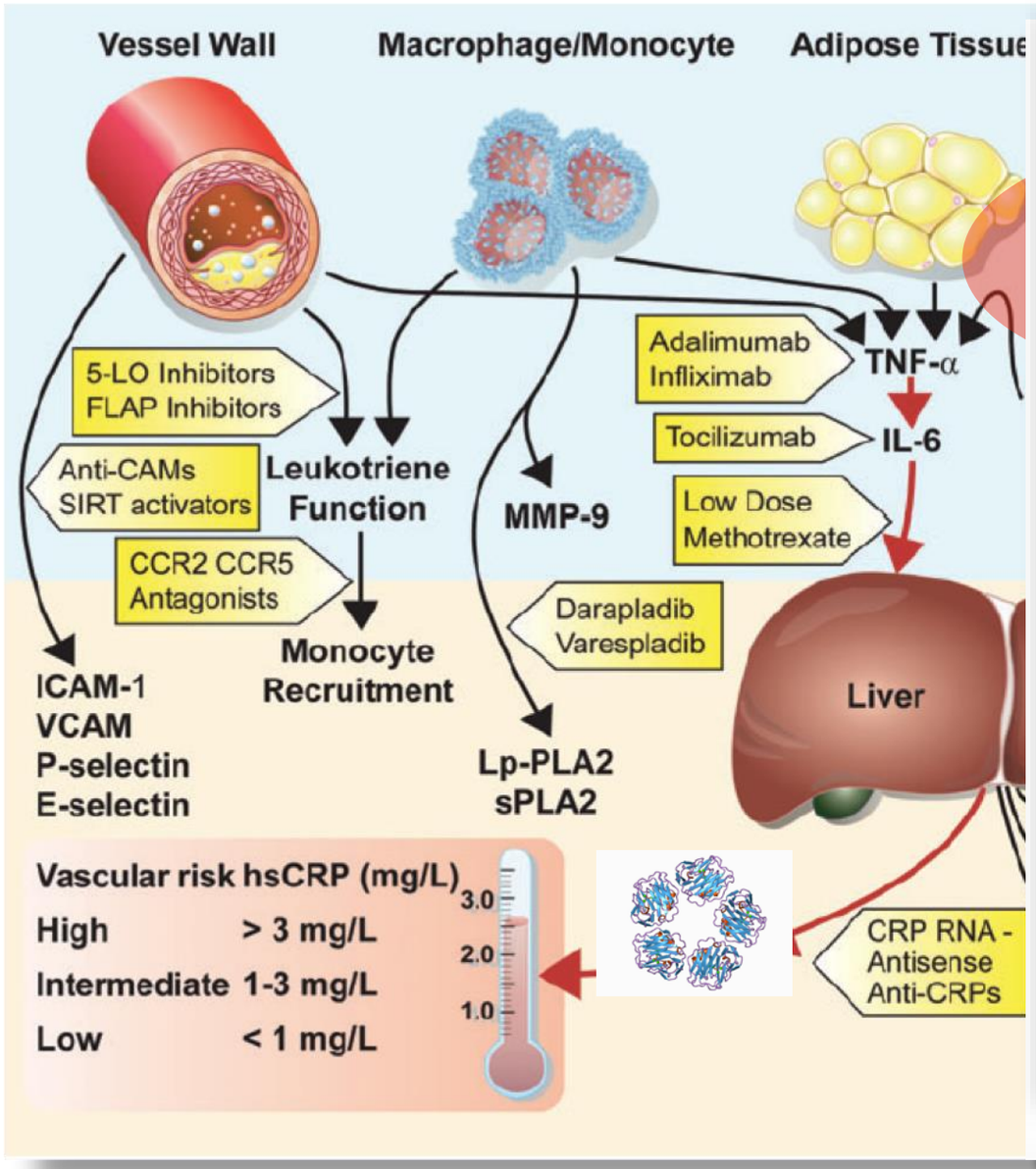


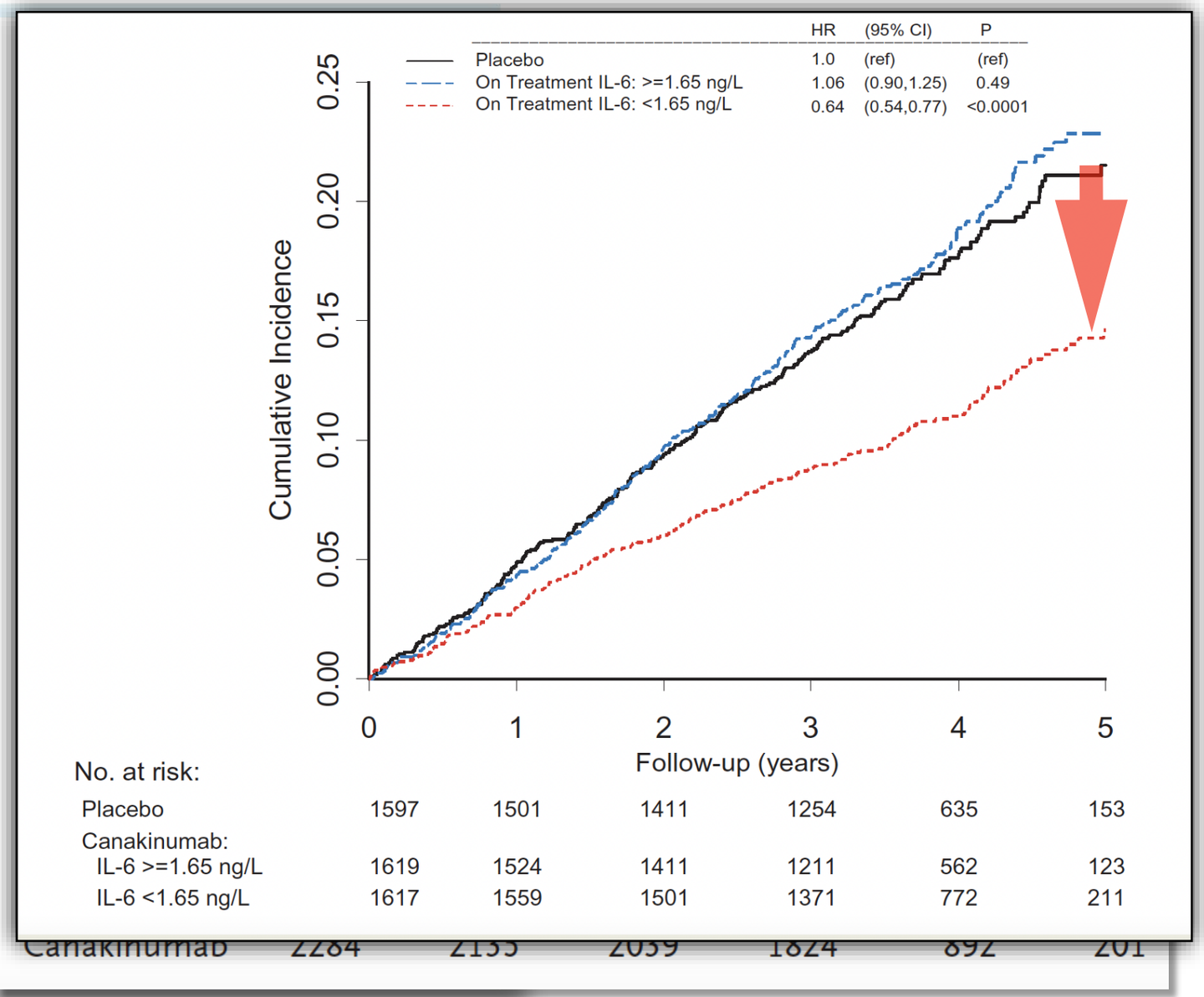
Antigen - Antibody Interaction



Infliximab

Learning from Nature:
Taking Advantage of the Immunsystem





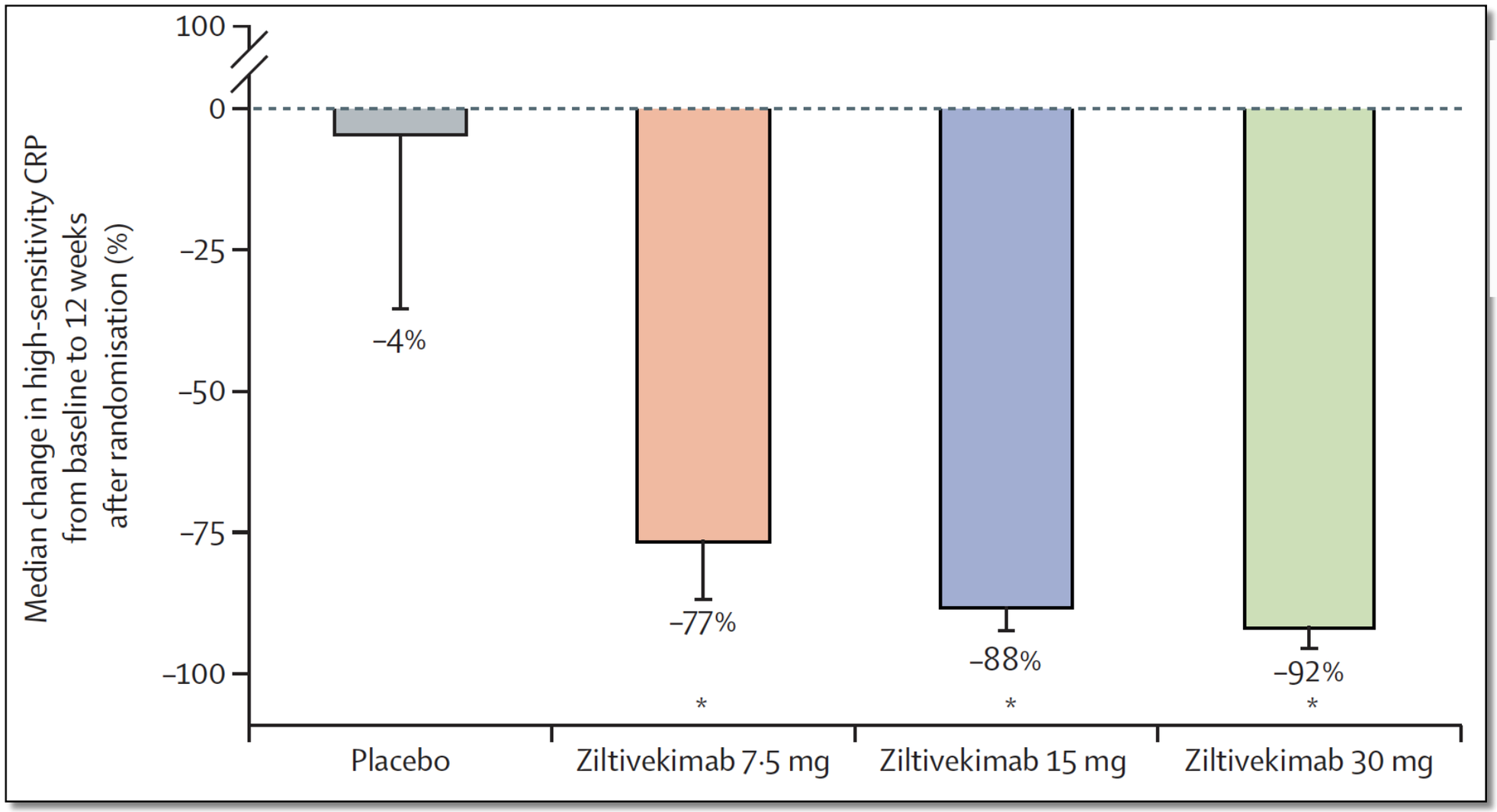
Paul Ridker and Thomas F. Lüscher. Eur. Heart J. 2019

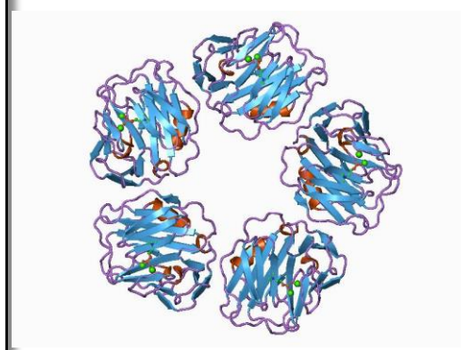
ESC European Society of Cardiology

CRT "The Revolution in Pharmacotheraly" - Rome 31st January and 1st February 2024

IL-6 inhibition with ziltivekimab in patients at high atherosclerotic risk (RESCUE): a double-blind, randomised, placebo-controlled, phase 2 trial

*Paul M Ridker, Matt Devalaraja, Florian M M Baeres, Mads D M Engelmann, G Kees Hovingh, Milana Ivkovic, Larry Lo, Douglas Kling, Pablo Pergola, Dominic Raj, Peter Libby, Michael Davidson, on behalf of the RESCUE Investigators**



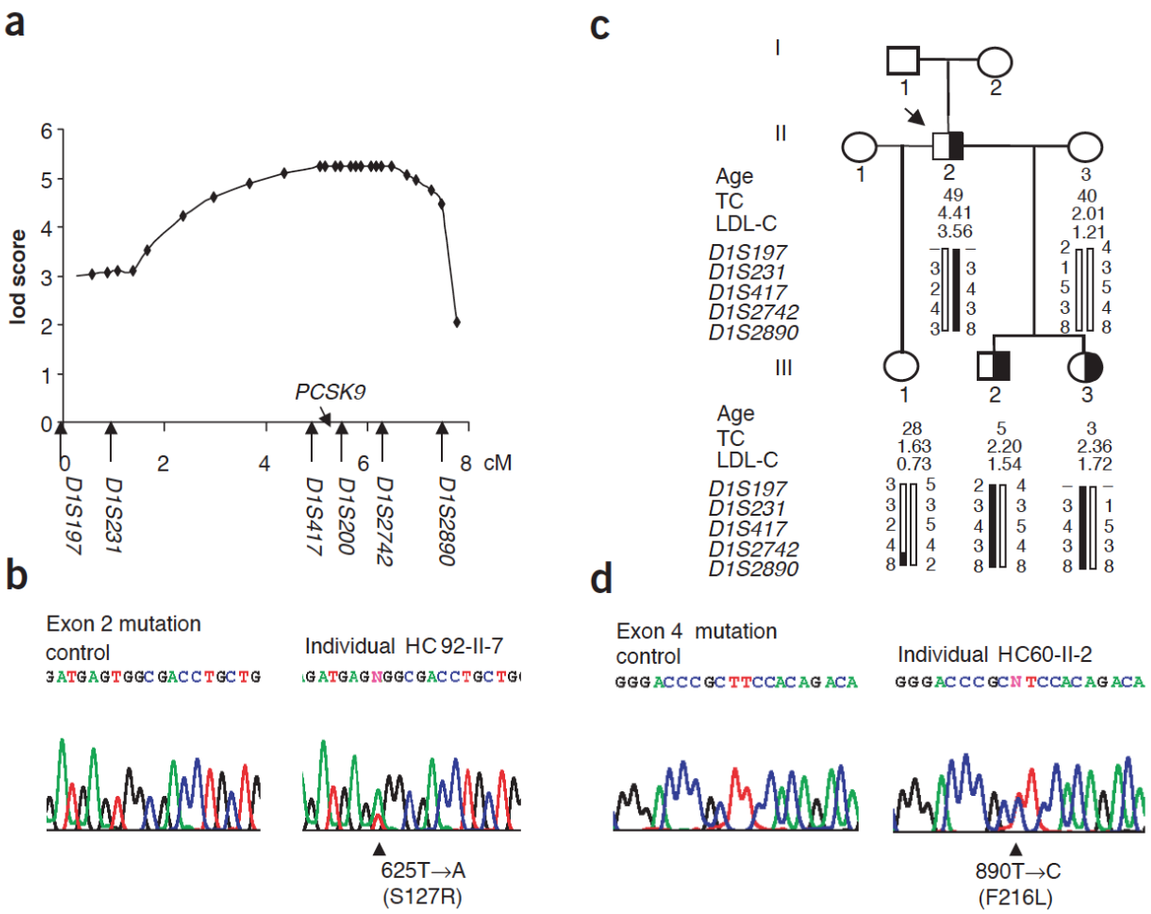


Lancet 2021; 397: 2060–69

Mutations in *PCSK9* cause autosomal dominant hypercholesterolemia

Marianne Abifadel[1,2], Mathilde Varret[1], Jean-Pierre Rabès[1,3], Delphine Allard[1], Khadija Ouguerram[4], Martine Devillers[1], Corinne Cruaud[5], Suzanne Benjannet[6], Louise Wickham[6], Danièle Erlich[1], Aurélie Derré[1], Ludovic Villéger[1], Michel Farnier[7], Isabel Beucler[8], Eric Bruckert[9], Jean Chambaz[10], Bernard Chanu[11], Jean-Michel Lecerf[12], Gerald Luc[12], Philippe Moulin[13], Jean Weissenbach[5], Annick Prat[6], Michel Krempf[4], Claudine Junien[1,3], Nabil G Seidah[6] & Catherine Boileau[1,3]

Autosomal dominant hypercholesterolemia (ADH; OMIM144400), a risk factor for coronary heart disease, is characterized by an increase in low-density lipoprotein cholesterol levels that is associated with mutations in the genes *LDLR* (encoding low-density lipoprotein receptor) or *APOB* (encoding apolipoprotein B). We mapped a third locus associated with ADH, *HCHOLA3* at 1p32, and now report two mutations in the gene *PCSK9* (encoding proprotein convertase subtilisin/kexin type 9) that cause ADH. *PCSK9* encodes NARC-1 (neural apoptosis regulated convertase), a newly identified human subtilase that is highly expressed in the liver and contributes to cholesterol homeostasis.

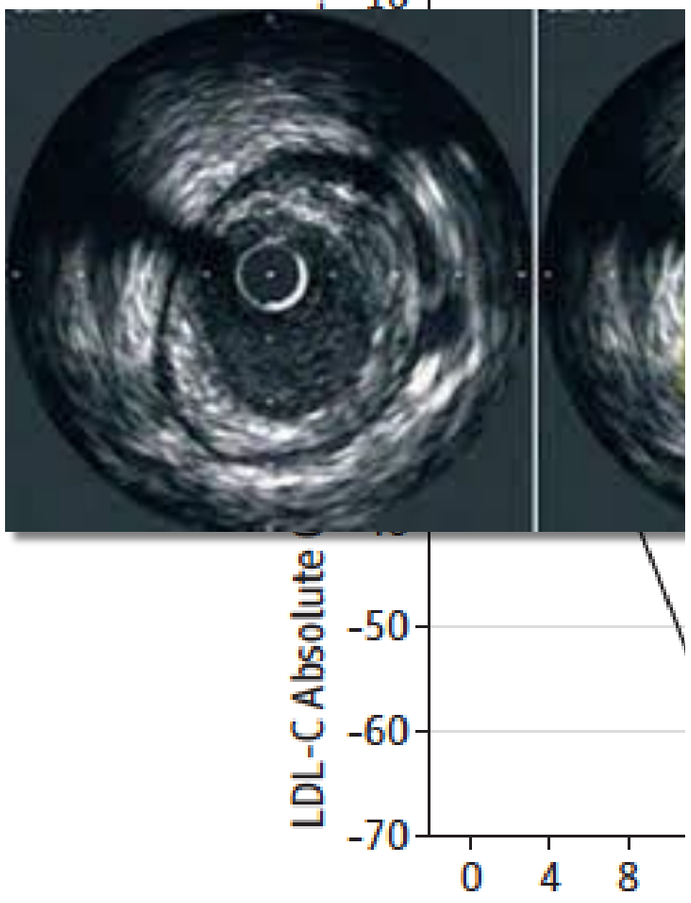


JAMA | Original Investigation

Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients
The GLAGOV Randomized Clinical Trial

Stephen J. Nicholls, MBBS, PhD; Rishi Puri, MBBS, PhD; Todd Anderson, MD; Christie M. Ballantyne, MD; Leslie Cho, MD; John J. P. Kastelein, MD, PhD; Wolfgang Koenig, MD; Ransi Somaratne, MD; Helina Kassahun, MD; Jingyuan Yang, PhD; Scott M. Wasserman, MD; Robert Scott, MD; Imre Ungi, MD, PhD; Jakub Podolec, MD, PhD; Antonius Oude Ophuis, MD, PhD; Jan H. Cornel, MD, PhD; Marilyn Borgman, RN, BSN; Danielle M. Brennan, MS; Steven E. Nissen, MD

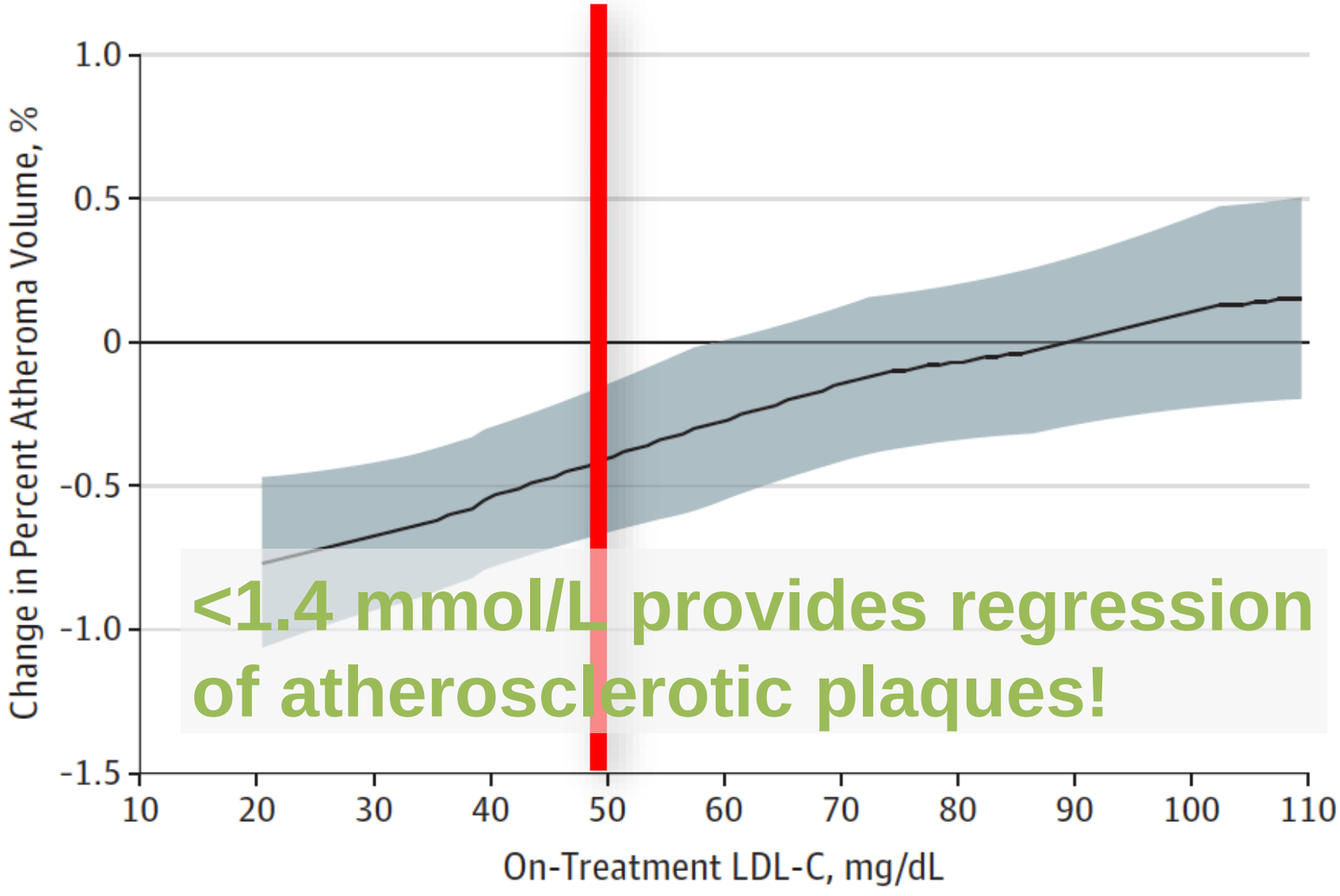
Figure 2. Mean Absolute Change

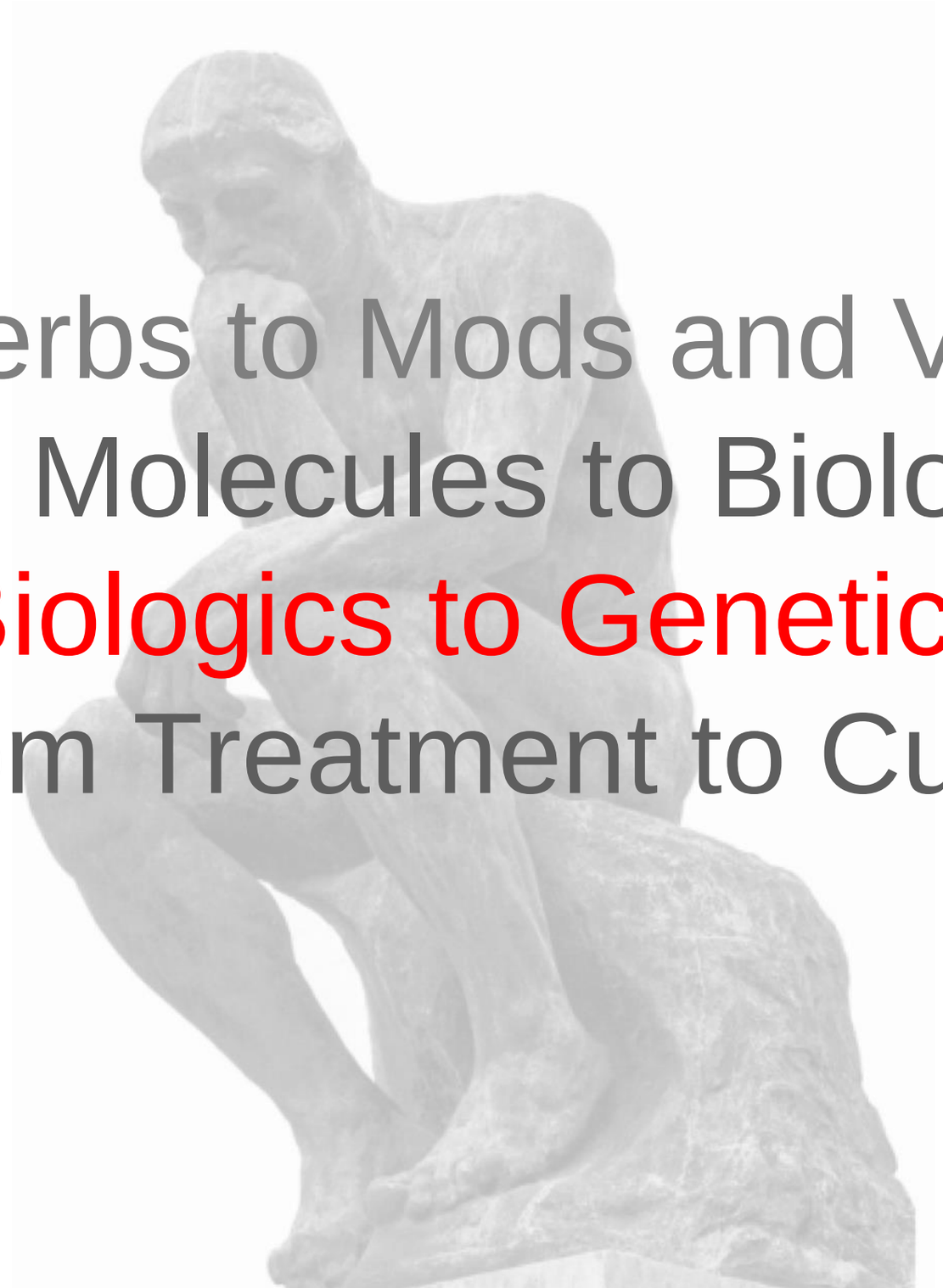


No. of patients

Placebo	484	4
Evolocumab	484	4

Figure 4. Post Hoc Analysis Examining the Relationship Between Achieved LDL-C Level and Change in Percent Atheroma Volume





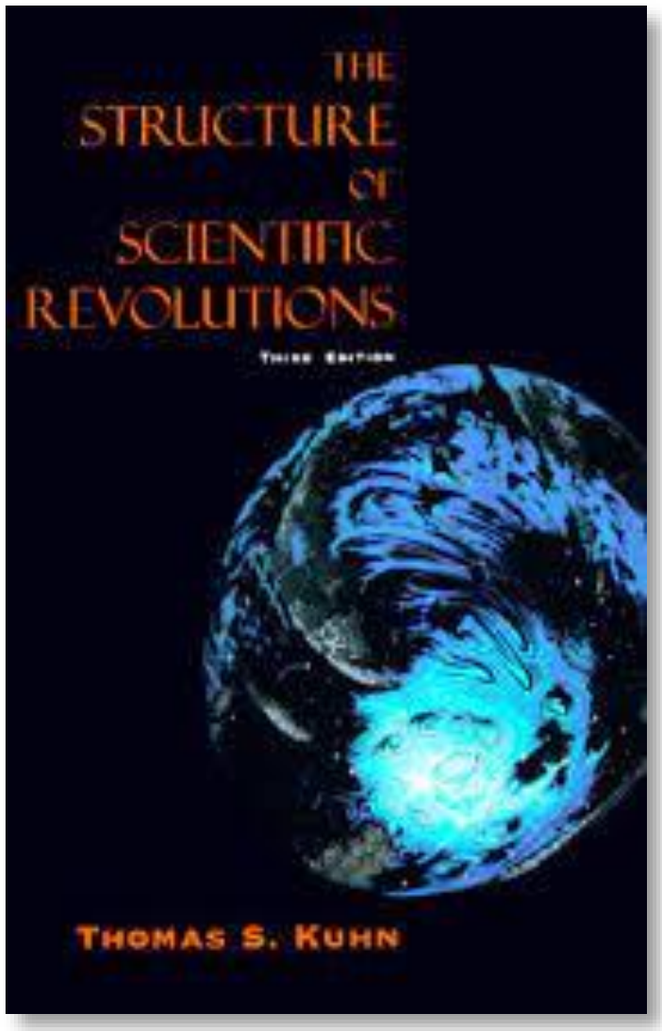
From Herbs to Mods and Venoms

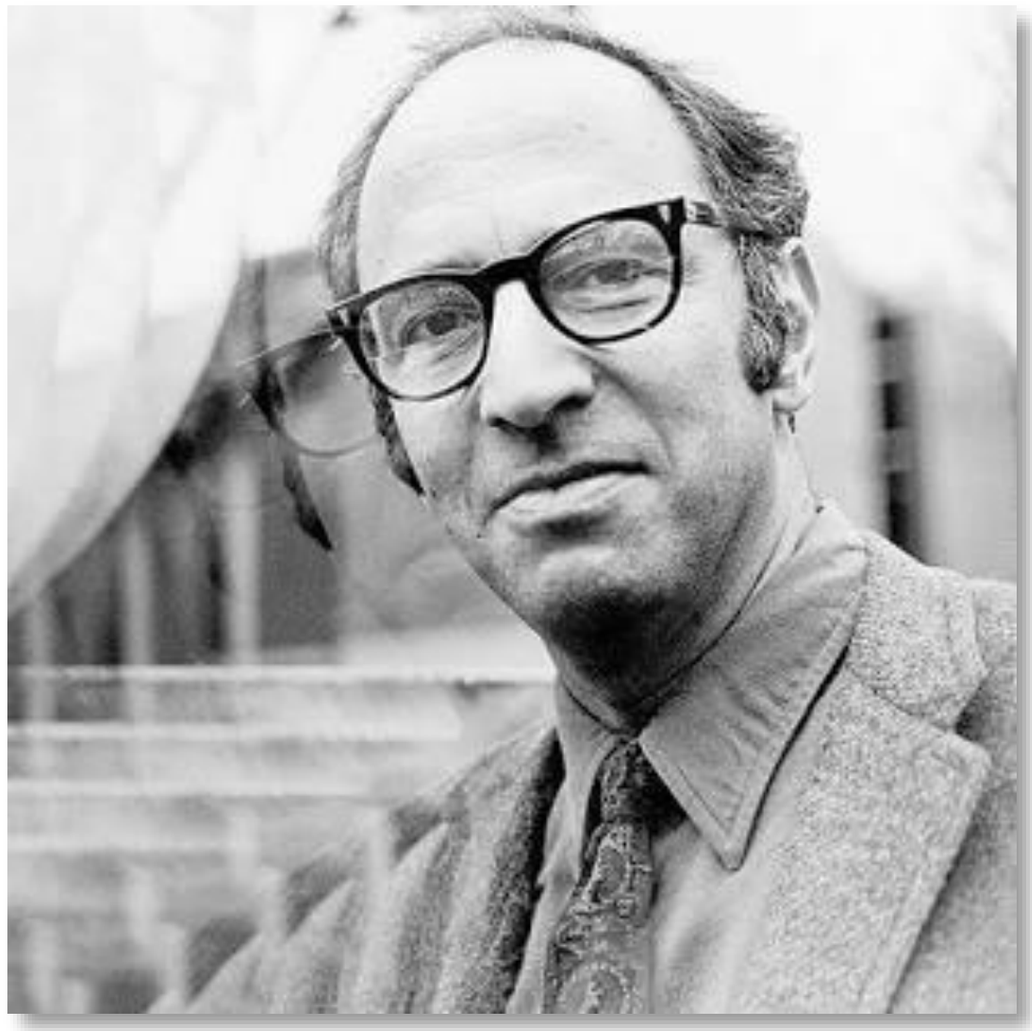
From Molecules to Biologics

From Biologics to Genetic Tools

From Treatment to Cure

A Revolution in Pharmacotherapy: From Herbs to pills to antobodies and genetic tools





A pradigm shift in the management of chronic diseases

The Nobel Prize in Physiology Medicine 2006

Photo: L. Cicero

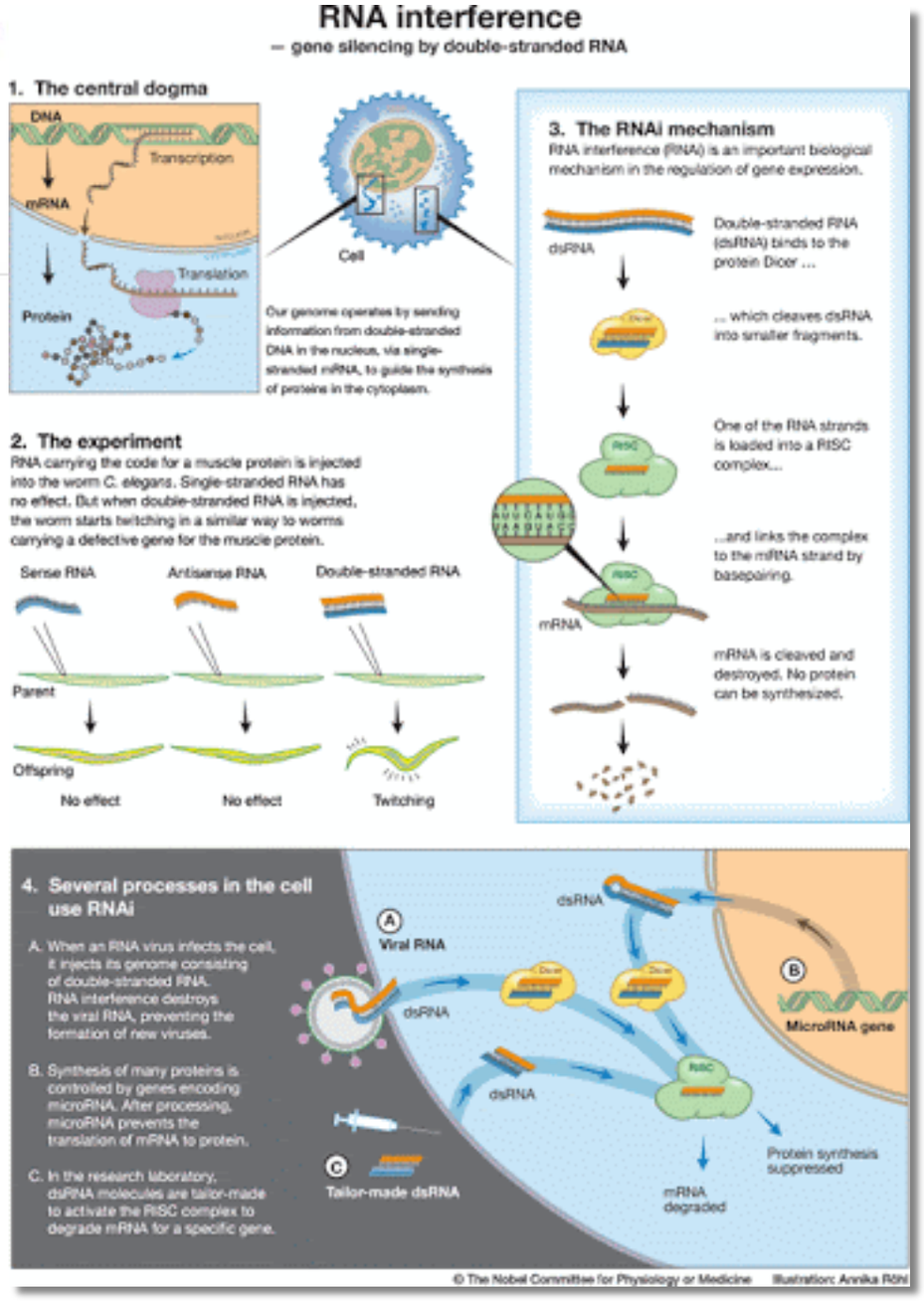
Andrew Z. Fire

Prize share: 1/2

Photo: J. Mottern

Craig C. Mello

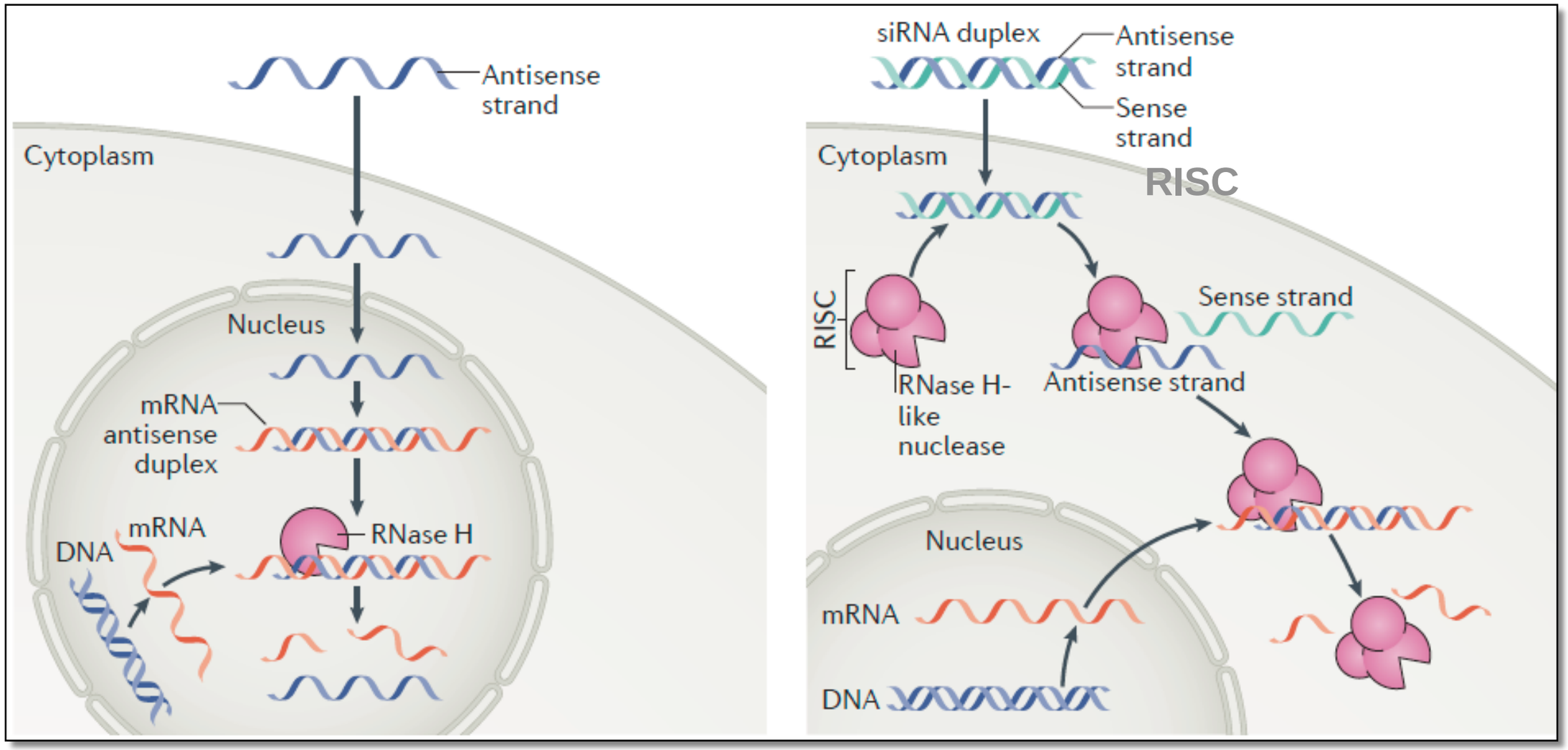
Prize share: 1/2



Revolution in Pharmacotherapy:ASO and siRNA

Antisense Technology

RNA Interference



RISC = **R**NA-**I**nduced **S**ilencing **C**omplex

Nordestgaard et al. Nature Rev. Cardiol. 2018;15: 261-272

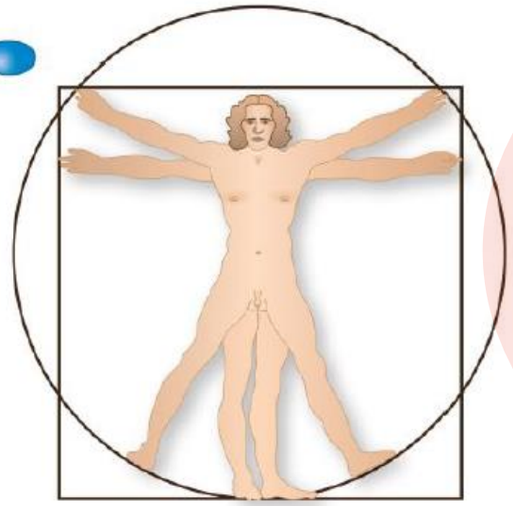
Subcutaneous injection

ASO drug

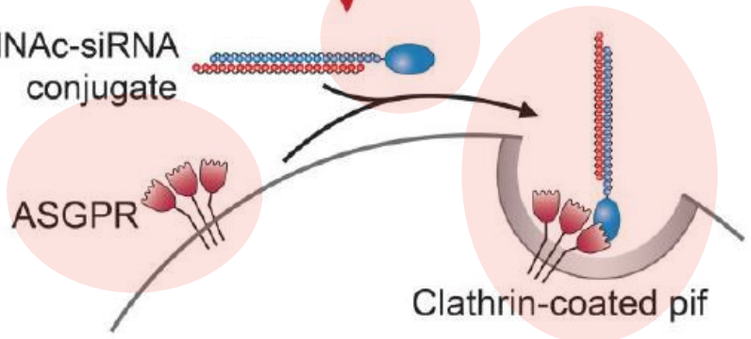
GalNAc-siRNA conjugate

siRNA drug

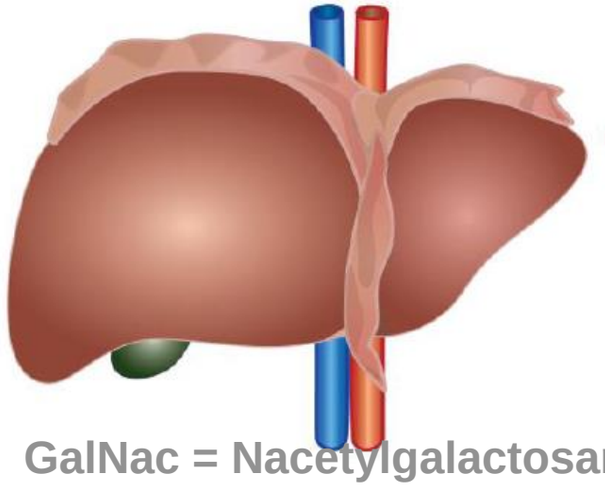
Transport through the circulation



GalNAc-siRNA conjugate



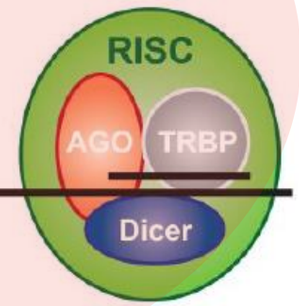
Selective entry into hepatocytes via receptor-mediated endocytosis



Intracellular release of siRNA from endosomes

siRNA drug

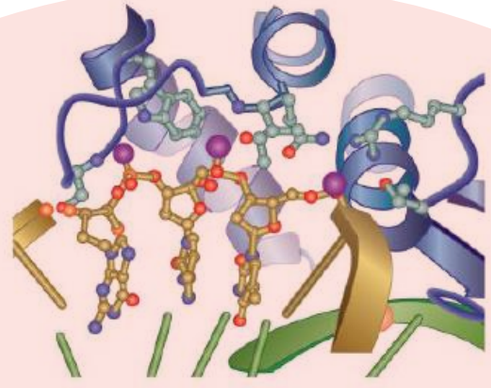
engineered siRNA forms highly stable complex with RISC



target mRNA

Intracellular release of ASO from endosomes

ASO drug



engineered ASO forms complex with RNAse H

RNAse H mediates target RNA cleavage

efficient and specific silencing of target gene

GalNac = Nacetylgalactosamine
ASGR = Asialoglycoprotein receptor

Ulf Landmesser et al. Eur. Heart J. 2020

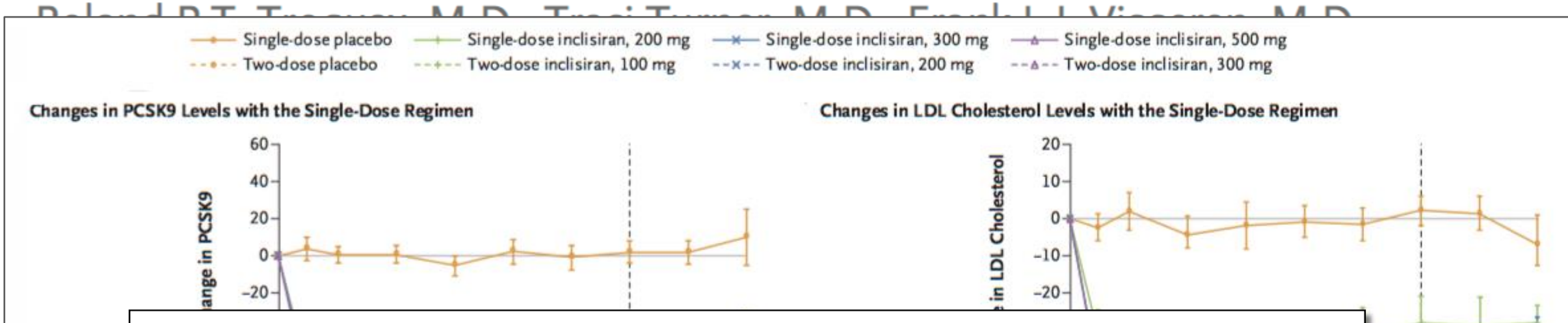
ESC European Society of Cardiology

CRT "The Revolution in Pharmacotheraly" - Rome 31st January and 1st February 2024

Inclisiran in Patients at High Cardiovascular Risk with Elevated LDL Cholesterol

Kausik K. Ray, M.D., Ulf Landmesser, M.D., Lawrence A. Leiter, M.D., David Kallend, M.D., Robert Dufour, M.D., Mahir Karakas, M.D., Tim Hall, M.D.,

RNA Interference is the Pharmaco-therapy of the Future

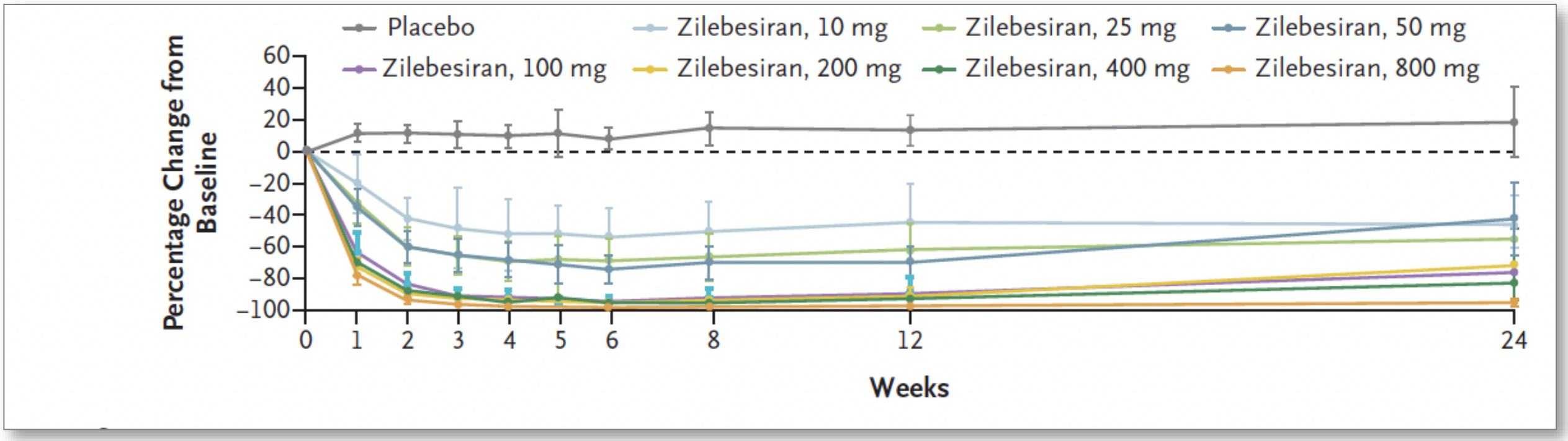


No. at Risk										
Single-dose placebo	65	64	65	62	64	65	62	64	61	14
Single-dose inclisiran, 200 mg	60	60	60	60	60	58	60	60	60	23
Single-dose inclisiran, 300 mg	61	60	61	61	61	61	60	60	59	19
Single-dose inclisiran, 500 mg	65	65	64	62	64	61	63	61	59	28

No. at Risk										
Single-dose placebo	65	65	65	62	64	65	62	64	62	27
Single-dose inclisiran, 200 mg	60	60	59	60	60	58	60	60	60	49
Single-dose inclisiran, 300 mg	61	61	61	61	60	61	60	60	61	50
Single-dose inclisiran, 500 mg	65	65	65	62	64	60	63	60	61	57

Zilebesiran, an RNA Interference Therapeutic Agent for Hypertension

Akshay S. Desai, M.D., M.P.H., David J. Webb, M.D., D.Sc., Jorg Taubel, M.D., Sarah Casey, M.B., Ch.B., Yansong Cheng, Ph.D., Gabriel J. Robbie, Ph.D., Don Foster, M.S., Stephen A. Huang, M.D., Sean Rhyee, M.D., M.P.H., Marianne T. Sweetser, M.D., Ph.D., and George L. Bakris, M.D.



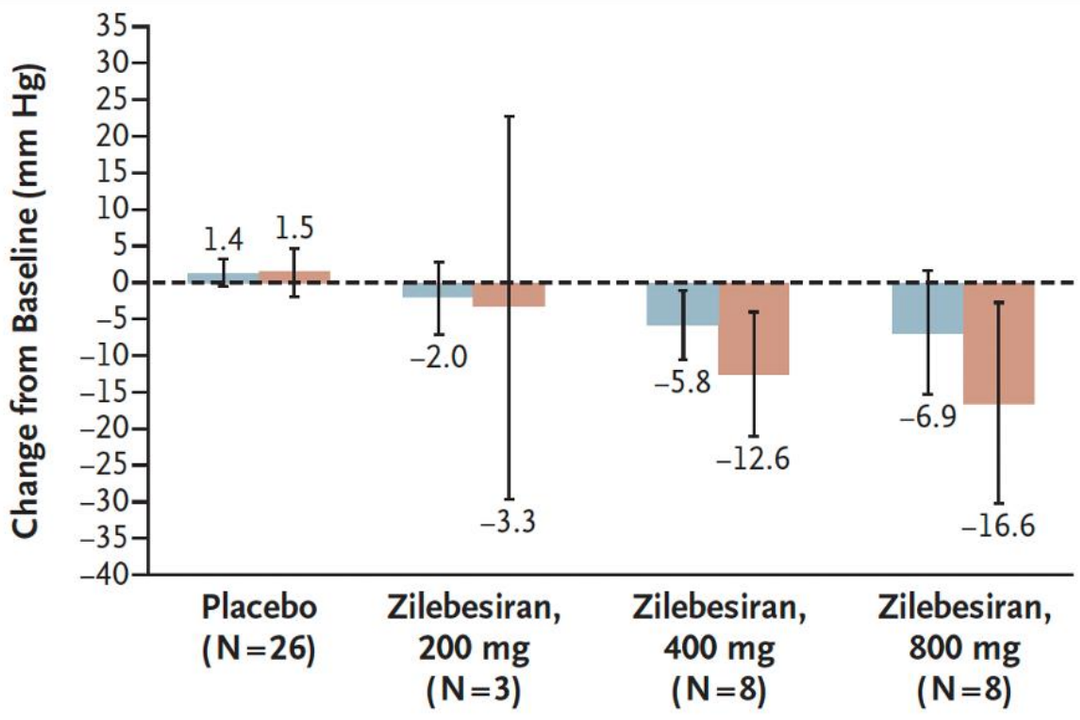
N Engl J Med 2023;389:228-38

Zilebesiran, an RNA Interference Therapeutic Agent for Hypertension

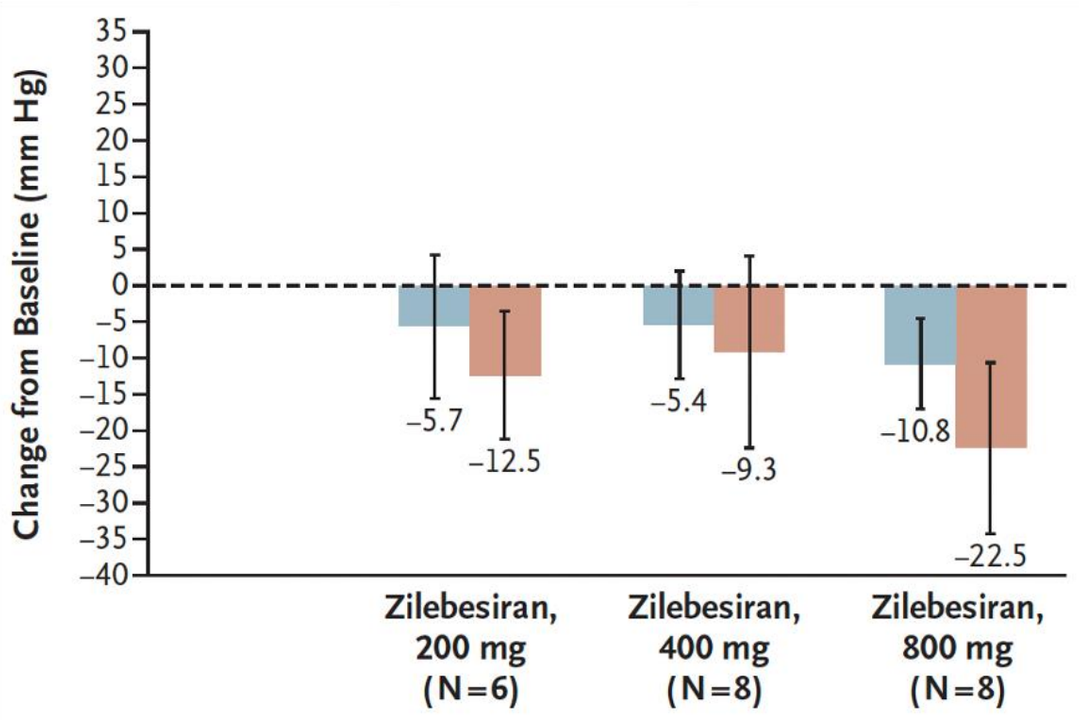
Akshay S. Desai, M.D., M.P.H., David J. Webb, M.D., D.Sc., Jorg Taubel, M.D., Sarah Casey, M.B., Ch.B., Yansong Cheng, Ph.D., Gabriel J. Robbie, Ph.D., Don Foster, M.S., Stephen A. Huang, M.D., Sean Rhyee, M.D., M.P.H., Marianne T. Sweetser, M.D., Ph.D., and George L. Bakris, M.D.

N Engl J Med 2023;389:228-38

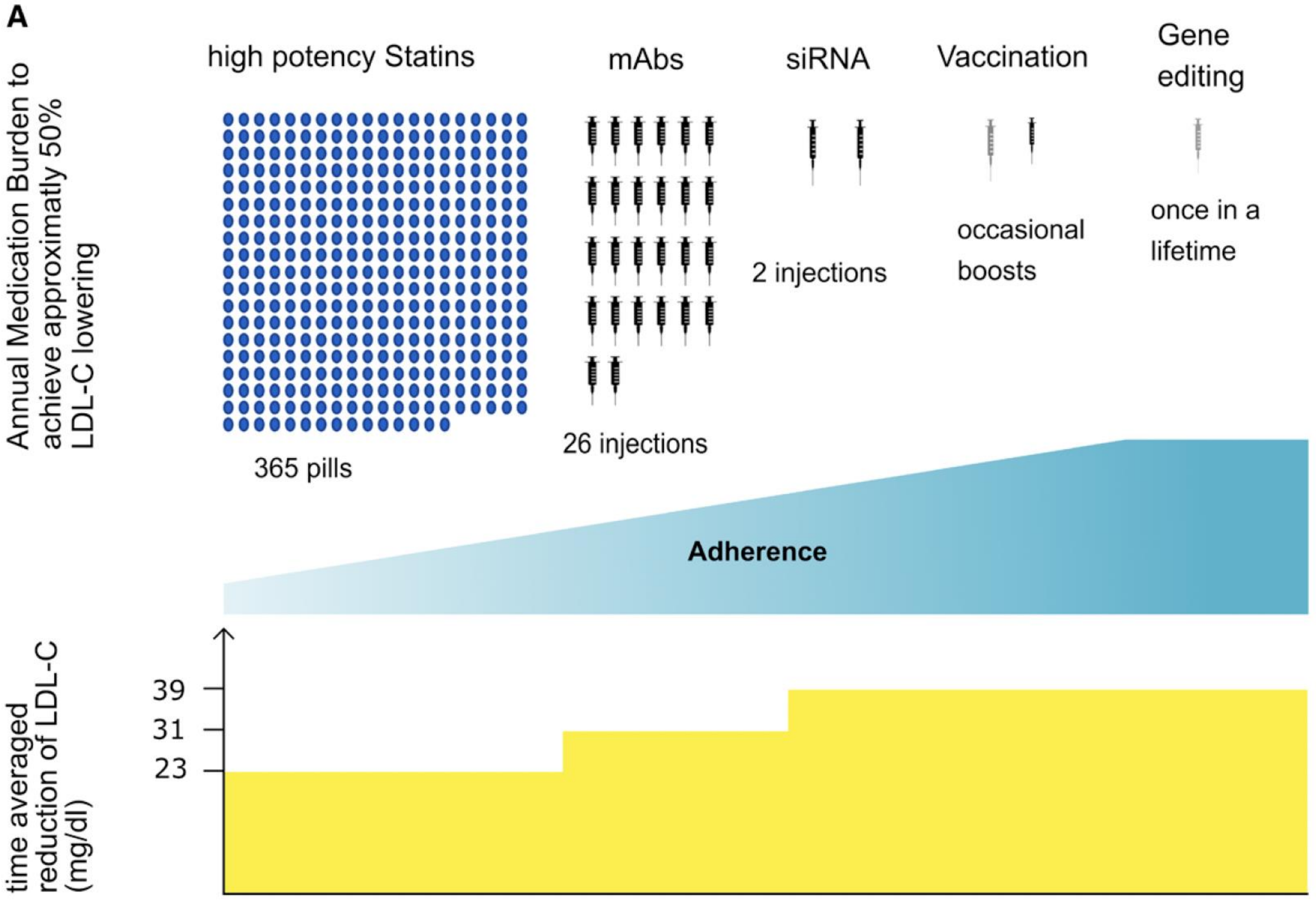
Blood Pressure Decrease at 6 weeks

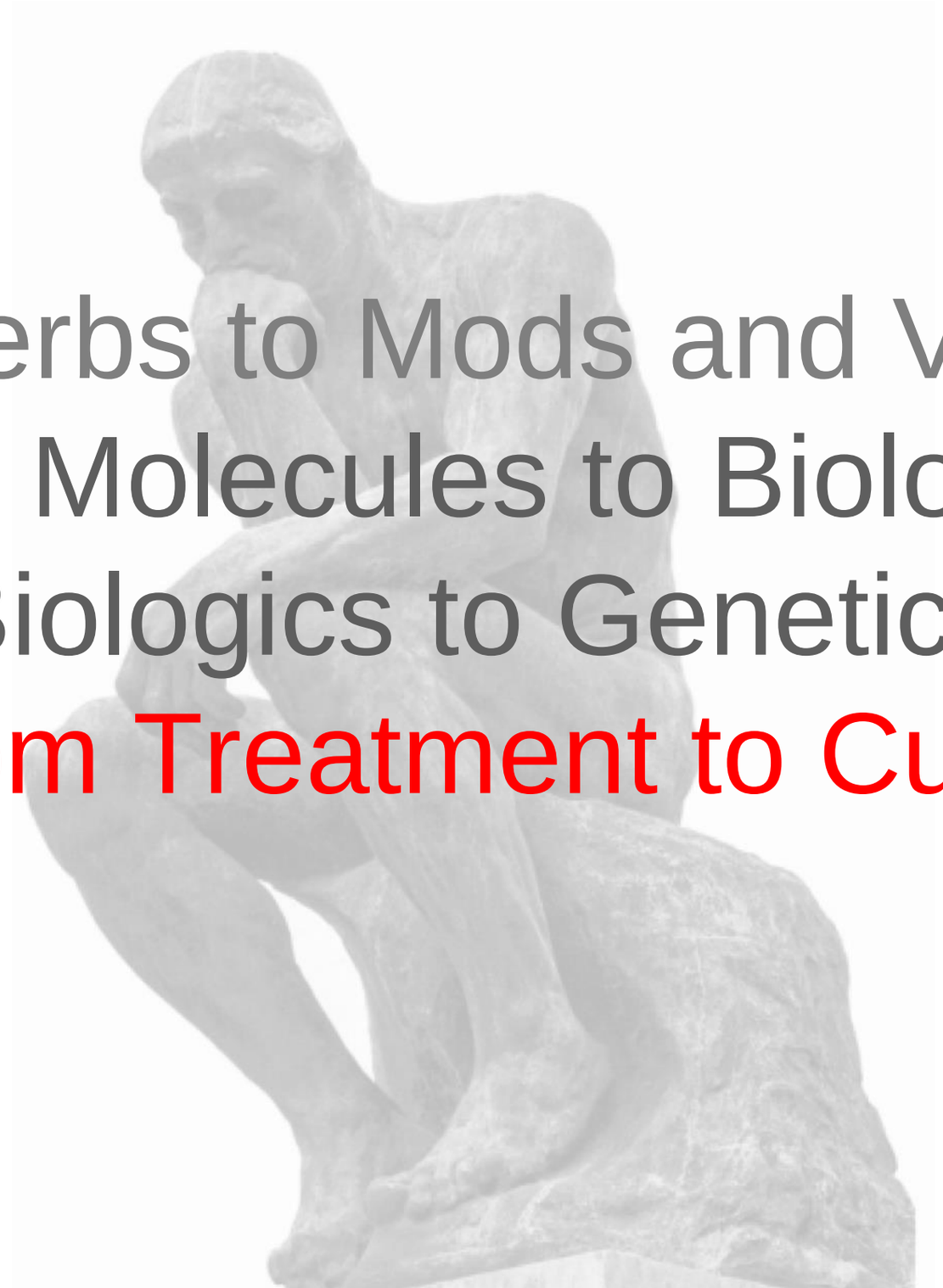


Blood Pressure Decrease at 24 weeks



From Pills to Nucleotidic Acids and Vaccination: Compliance and Efficacy





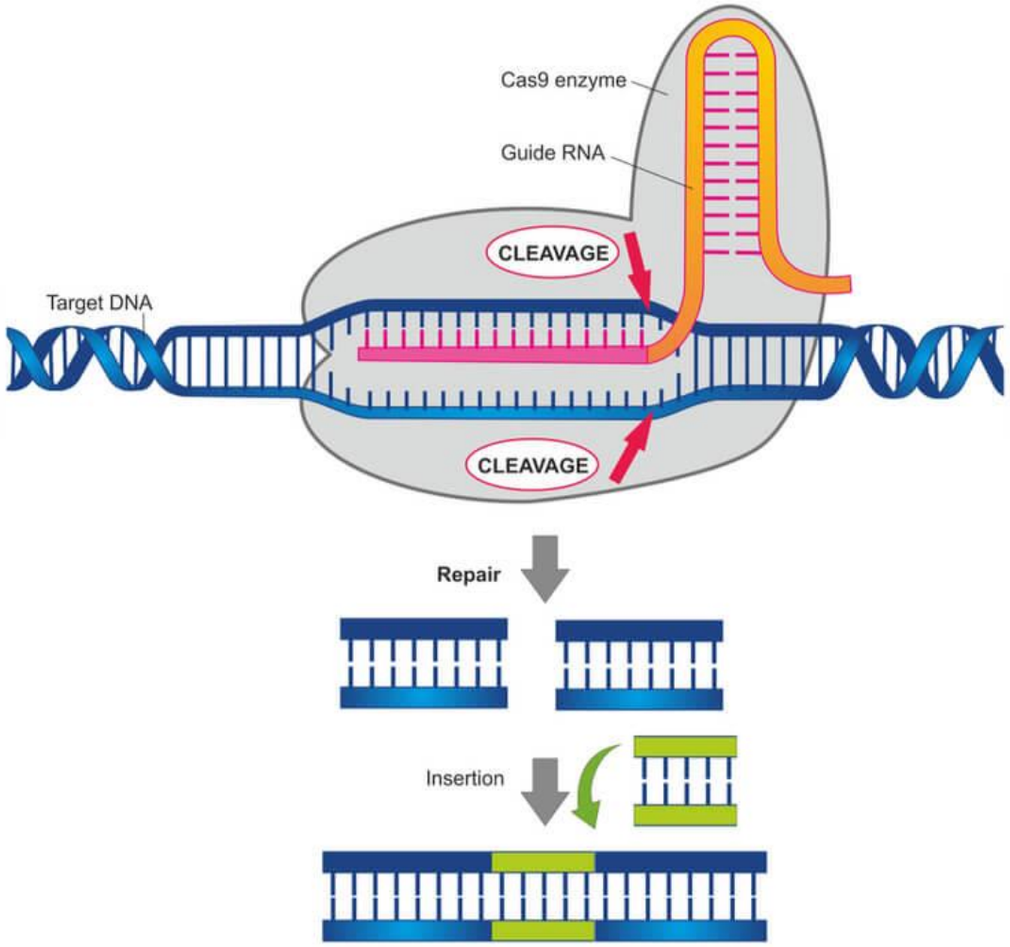
From Herbs to Mods and Venoms
From Molecules to Biologics
From Biologics to Genetic Tools
From Treatment to Cure

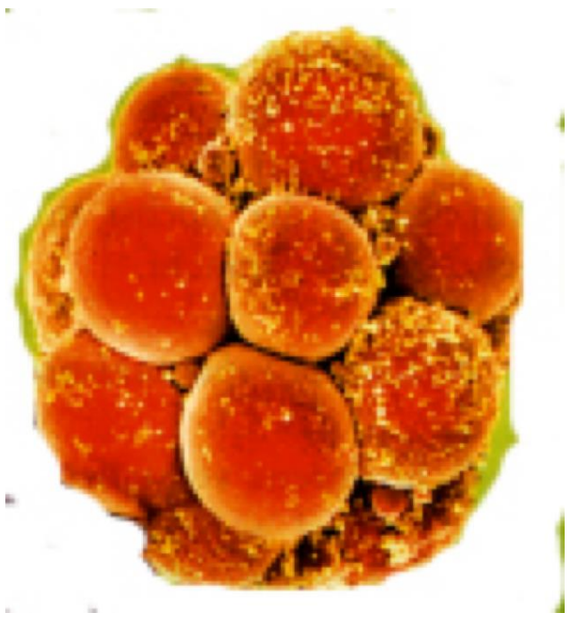
Learning from Nature: Exchanging Genes:

Emmanuelle Charpentier and Jennifer Doudna

Crisper Cas 9:
The Gene Scissor

Clustered **R**egularly **I**nterspaced **S**hort **P**alindromic **R**epeats



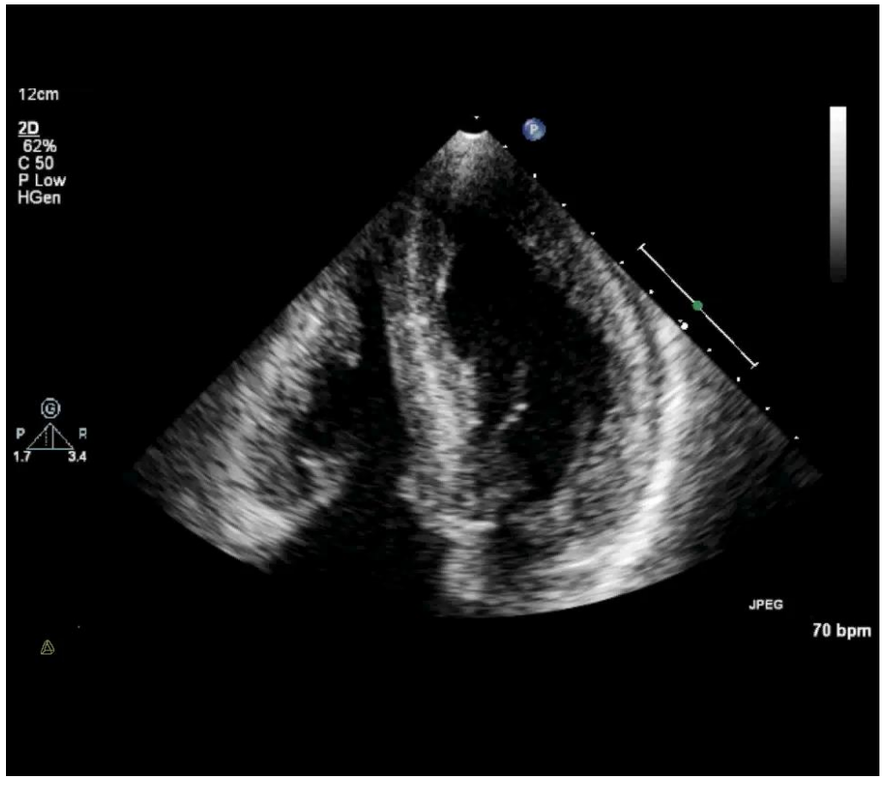


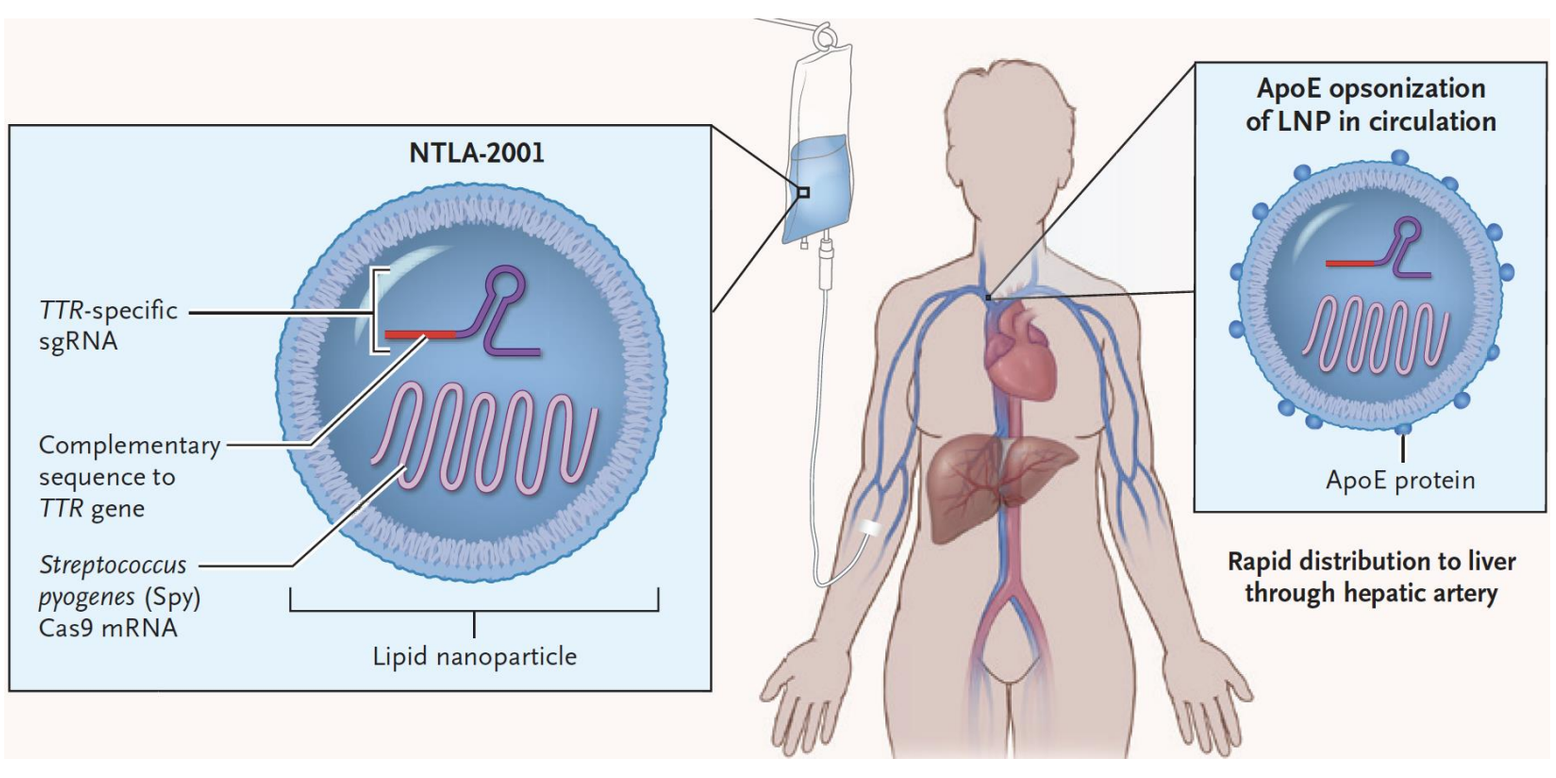
ESC European Society of Cardiology

CRT "The Revolution in Pharmacotheraly" - Rome 31st January and 1st February 2024

CRISPR-Cas9 In Vivo Gene Editing for Transthyretin Amyloidosis

Julian D. Gillmore, M.D., Ph.D., Ed Gane, M.B., Ch.B., Jorg Taubel, M.D., Justin Kao, M.B., Ch.B., Marianna Fontana, M.D., Ph.D., Michael L. Maitland, M.D., Ph.D., Jessica Seitzer, B.S., Daniel O'Connell, Ph.D., Kathryn R. Walsh, Ph.D., Kristy Wood, Ph.D., Jonathan Phillips, Ph.D., Yuanxin Xu, M.D., Ph.D., Adam Amaral, B.A., Adam P. Boyd, Ph.D., Jeffrey E. Cehelsky, M.B.A., Mark D. McKee, M.D., Andrew Schiermeier, Ph.D., Olivier Harari, M.B., B.Chir., Ph.D., Andrew Murphy, Ph.D., Christos A. Kyratsous, Ph.D., Brian Zambrowicz, Ph.D., Randy Soltys, Ph.D., David E. Gutstein, M.D., John Leonard, M.D., Laura Sepp-Lorenzino, Ph.D., and David Lebwohl, M.D.



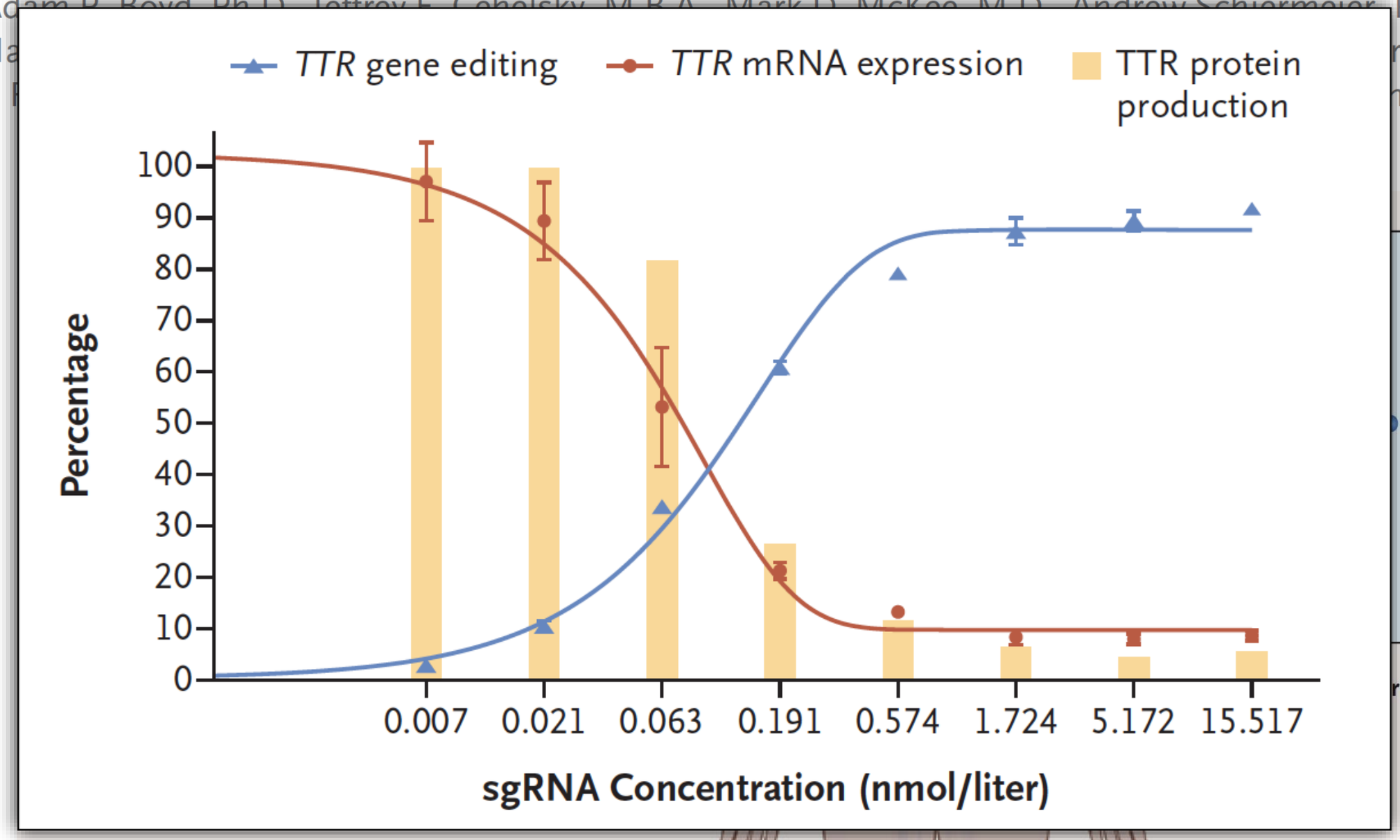


ESC European Society of Cardiology

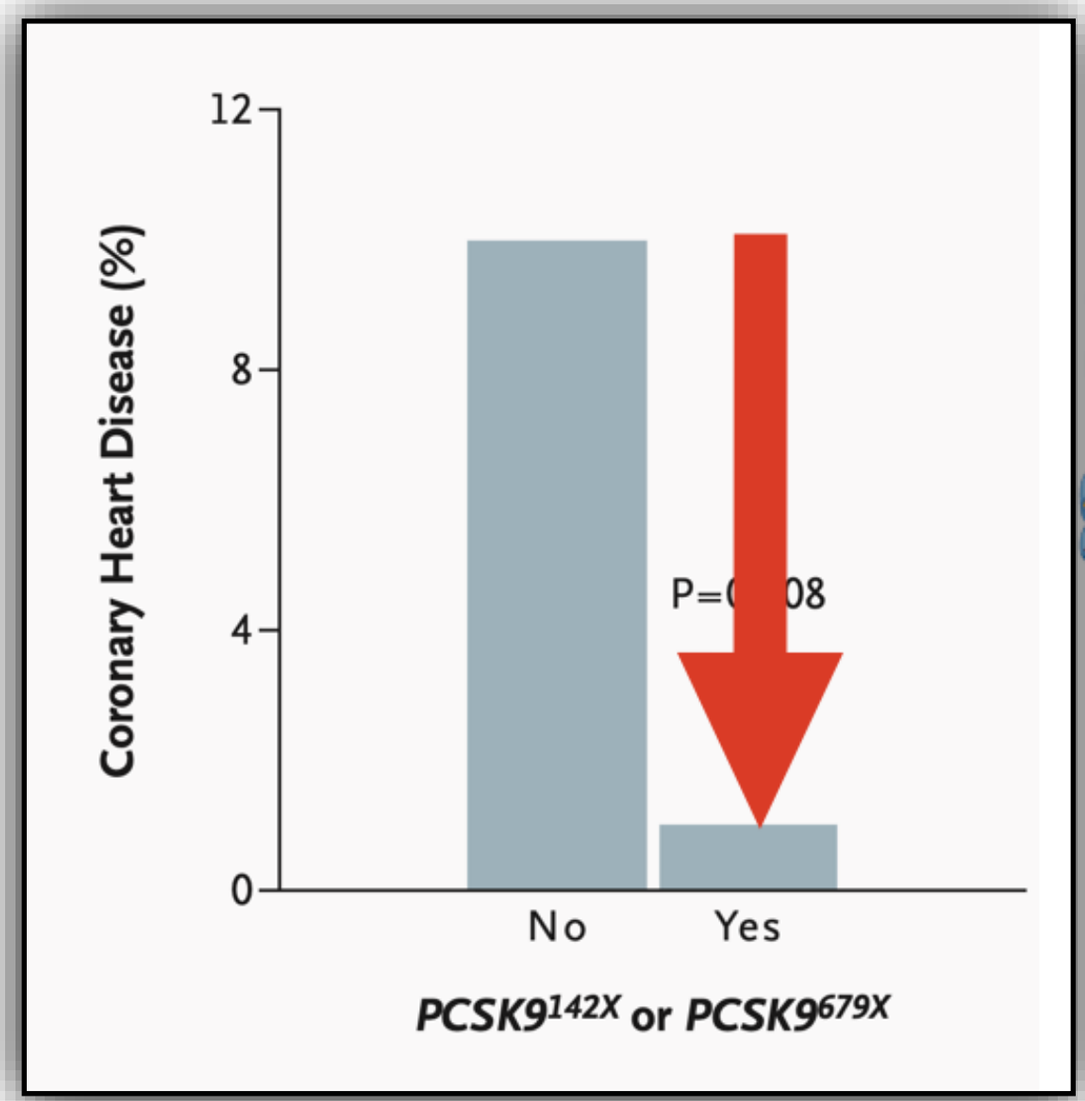
CRT "The Revolution in Pharmacotheraly" - Rome 31st January and 1st February 2024

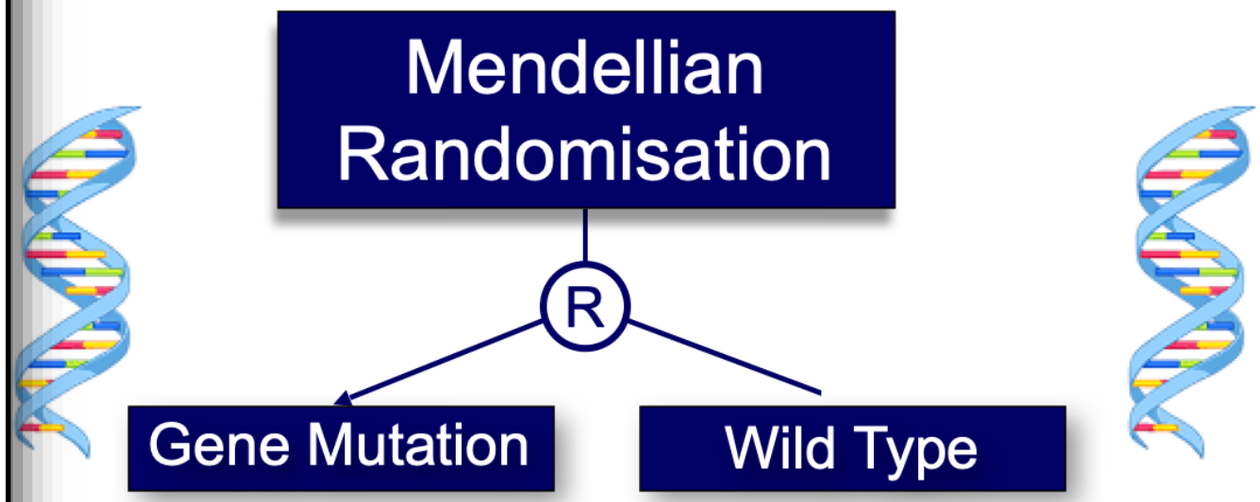
CRISPR-Cas9 In Vivo Gene Editing for Transthyretin Amyloidosis

Julian D. Gillmore, M.D., Ph.D., Ed Gane, M.B., Ch.B., Jorg Taubel, M.D., Justin Kao, M.B., Ch.B., Marianna Fontana, M.D., Ph.D., Michael L. Maitland, M.D., Ph.D., Jessica Seitzer, B.S., Daniel O'Connell, Ph.D., Kathryn R. Walsh, Ph.D., Kristy Wood, Ph.D., Jonathan Phillips, Ph.D., Yuanxin Xu, M.D., Ph.D., Adam Amaral, B.A., Ad[illegible] Ph.D., Olivier Ha[illegible]rowicz, Ph.D., [illegible].D.,



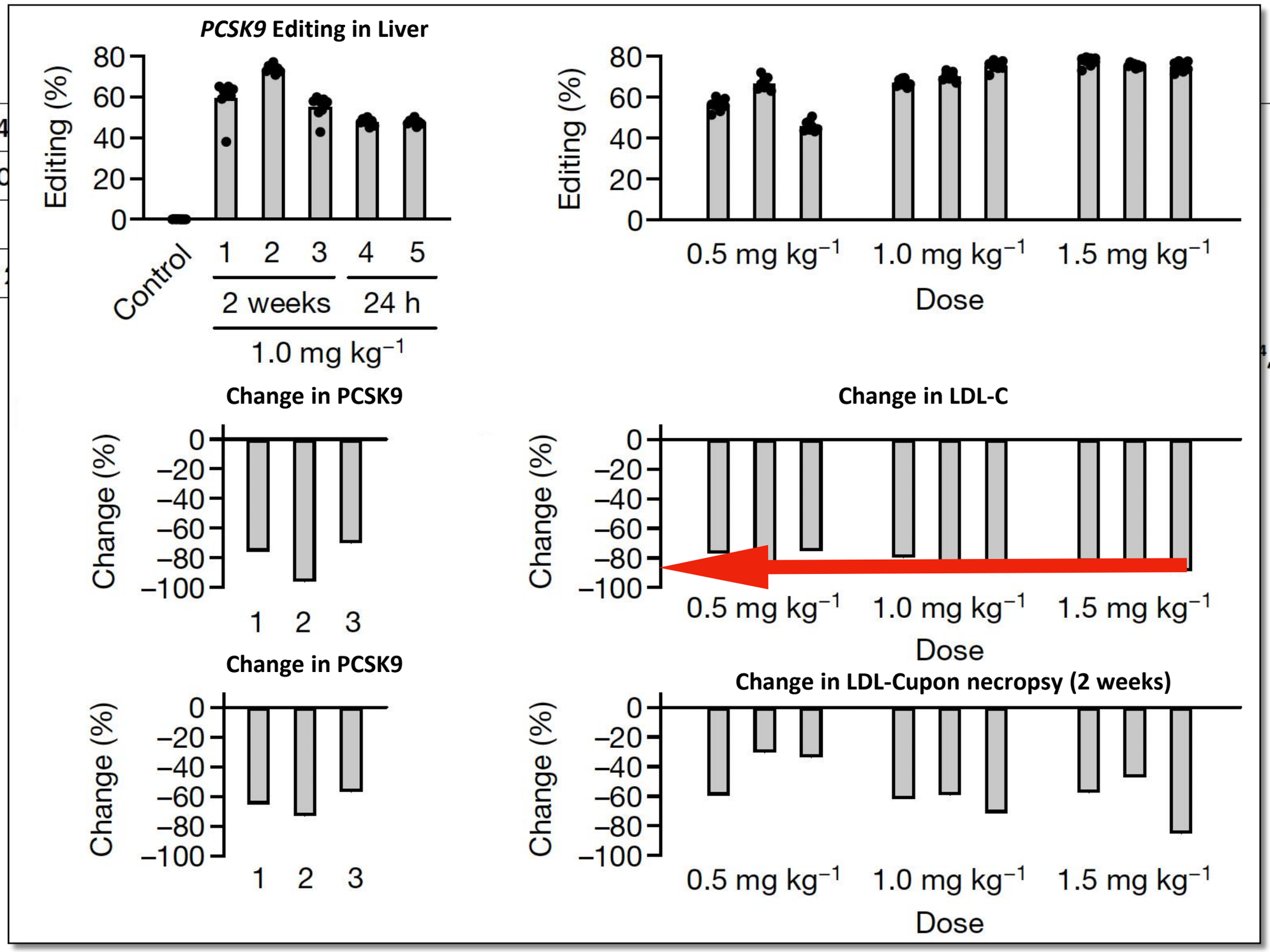
Mendellian Randomization in Atherosclerosis to prove causality





In vivo CRISPR base editing of *PCSK9* durably lowers cholesterol in primates

https://doi.org/10.1038/s4
Received: 6 December 20
Accepted: 11 April 2021
Published online: 19 May
Check for updates



The Future of Cardiology
Belgrade January 30th, 2024

SERBIAN ACADEMY
OF SCIENCES AND ARTS

Verve Therapeutics Announces Clearance of Investigational New Drug Application by the U.S. FDA for VERVE-101 in Patients with Heterozygous Familial Hypercholesterolemia

Gene Editing with CrisperCas9: From Treatment to Cure

We came from far……..

…….und we will get even further!