GLP-1 e Sistema Cardiovascolare: Fisiologia

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Disclosures

- Advisory Boards: AstraZeneca/BMS; Eli Lilly; Roche Diagnostics, Takeda
- Consultant: AstraZeneca/BMS; Boehringer Ingelheim; Lifescan; Merck Sharp & Dohme; Novo Nordisk; Sanofi
- Research Support: AstraZeneca/BMS; Eli Lilly; Lifescan; Sanofi; Takeda

GLP-1 RA and Vascular Outcomes in Type 2 Diabetes - 2016

HbA1c

MACE

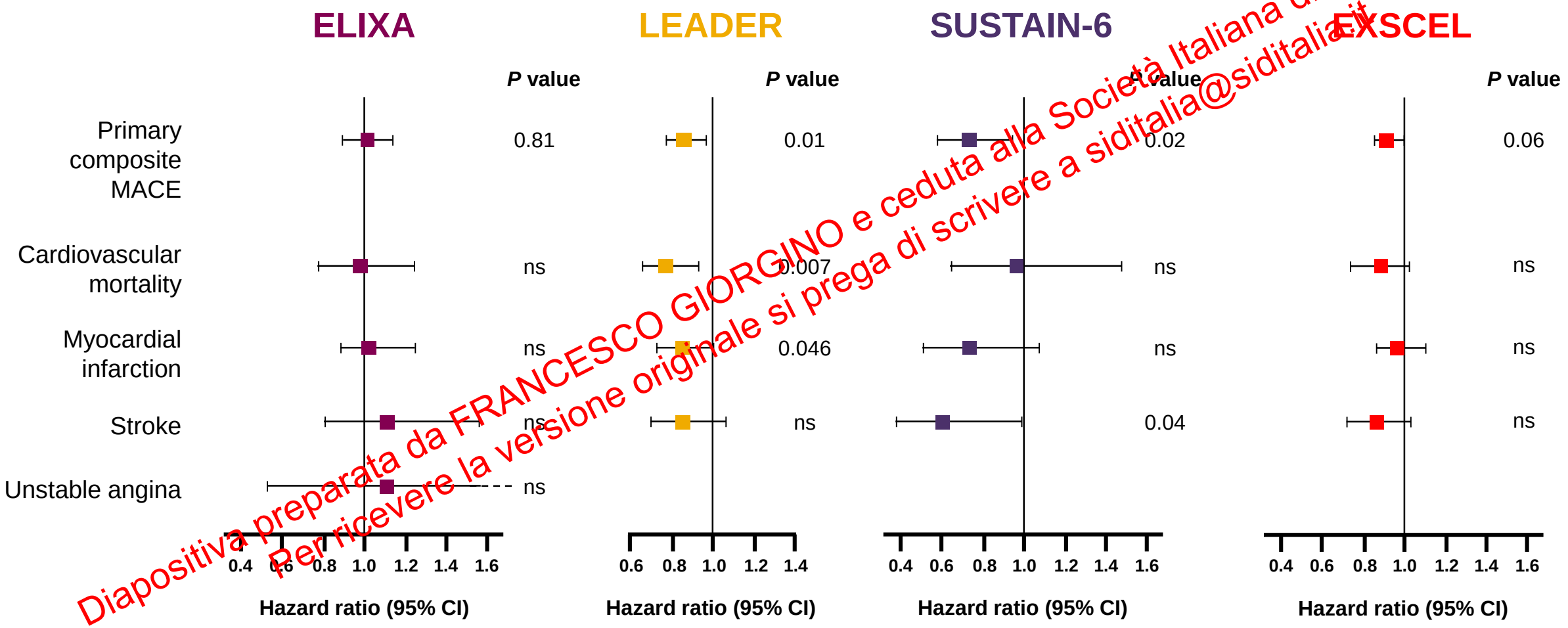
- CV Mortality
- Non-fatal MI
- Non-fatal Stroke

Renal Outcomes (AER, Nephropathy)

Lixisenatide | Liraglutide | Semaglutide

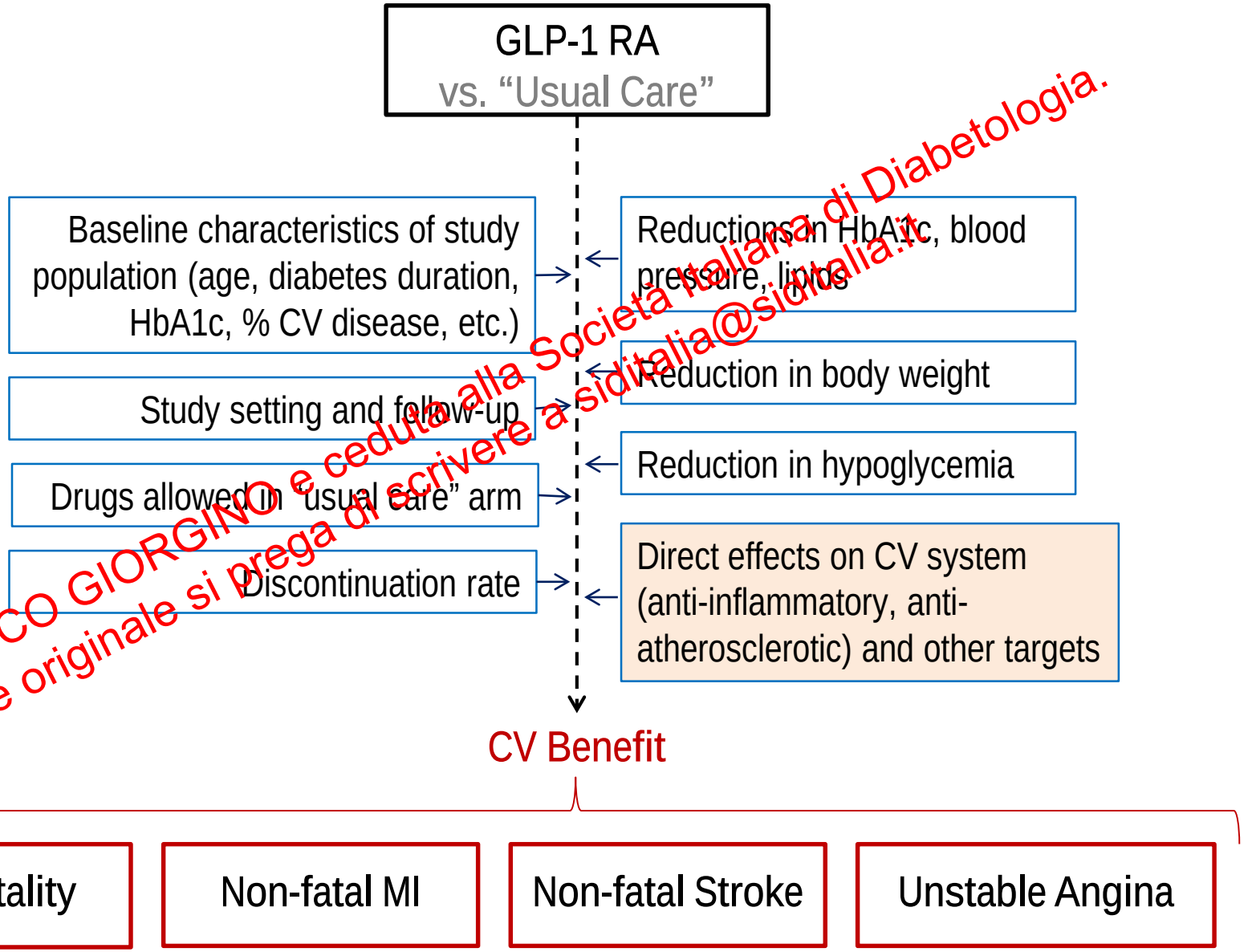
GLP-1 RA

Primary Endpoint and Its Individual Components in ELIXA, LEADER, SUSTAIN-6 and EXSCEL



CI, confidence interval; MACE, major adverse cardiovascular event; ns, not significant.
Adapted from Pfeffer MA, et al. *N Engl J Med* 2015;373:2247–2257; Marso SP, et al., *N Engl J Med* 2016;375:311-22; Marso SP, et al., *N Engl J Med* 2016 375:1834-1844; Holman RR et al., *N Engl J Med,* in press.

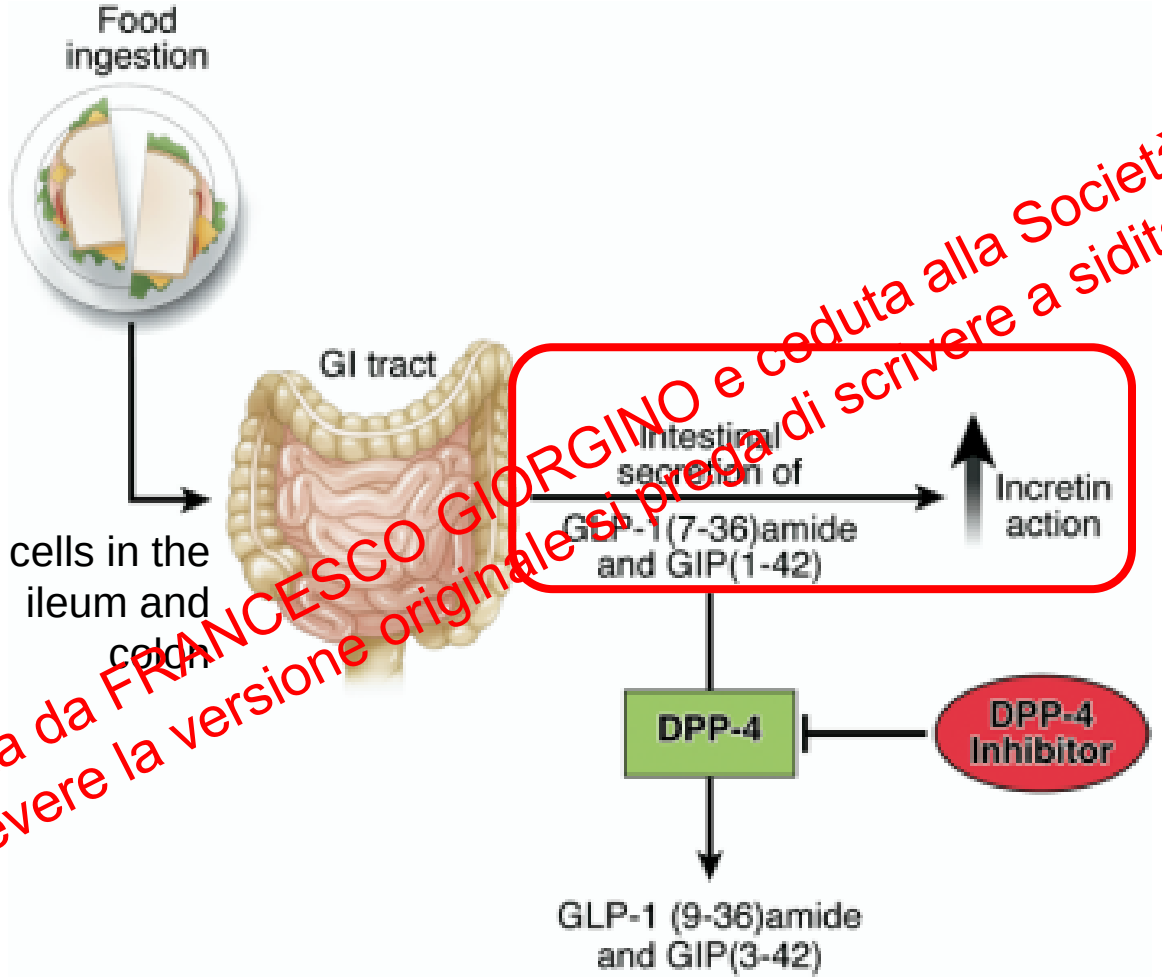
Potential Factors in CV Outcomes Trials with GLP-1 RAs



↓ **All**-cause Mortality

CV, cardiovascular; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; HF, heart failure; SGLT2-Is, sodium glucose transporter-2 inhibitors.

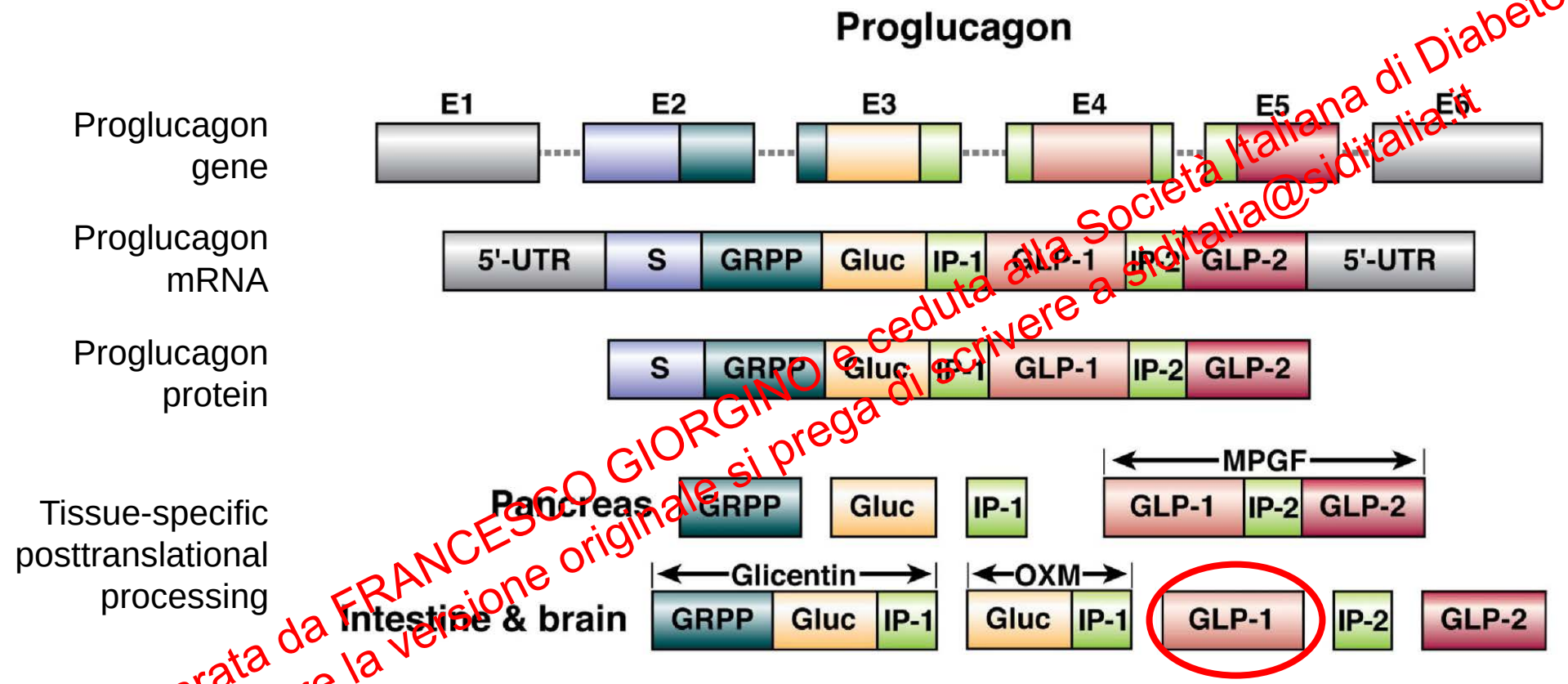
Glucagon-Like Pepetide-1 (GLP-1) Secretion



GIP, glucose-dependent insulinotropic polypeptide; DPP-4, dipeptidyl peptidase-4

Adapted from Baggio et al., Gastroeneterolgy, 2007

GLP-1 Derives from Proglucagon



GRPP: glicentin-related polypeptide; GLUC: Glucagon; IP-1: intervening peptide-1; MPGF: proglucagon fragment; OXM: oxyntomodulin; IP-2: intervening peptide-2

Baggio et al., Gastroenterolgy, 2007

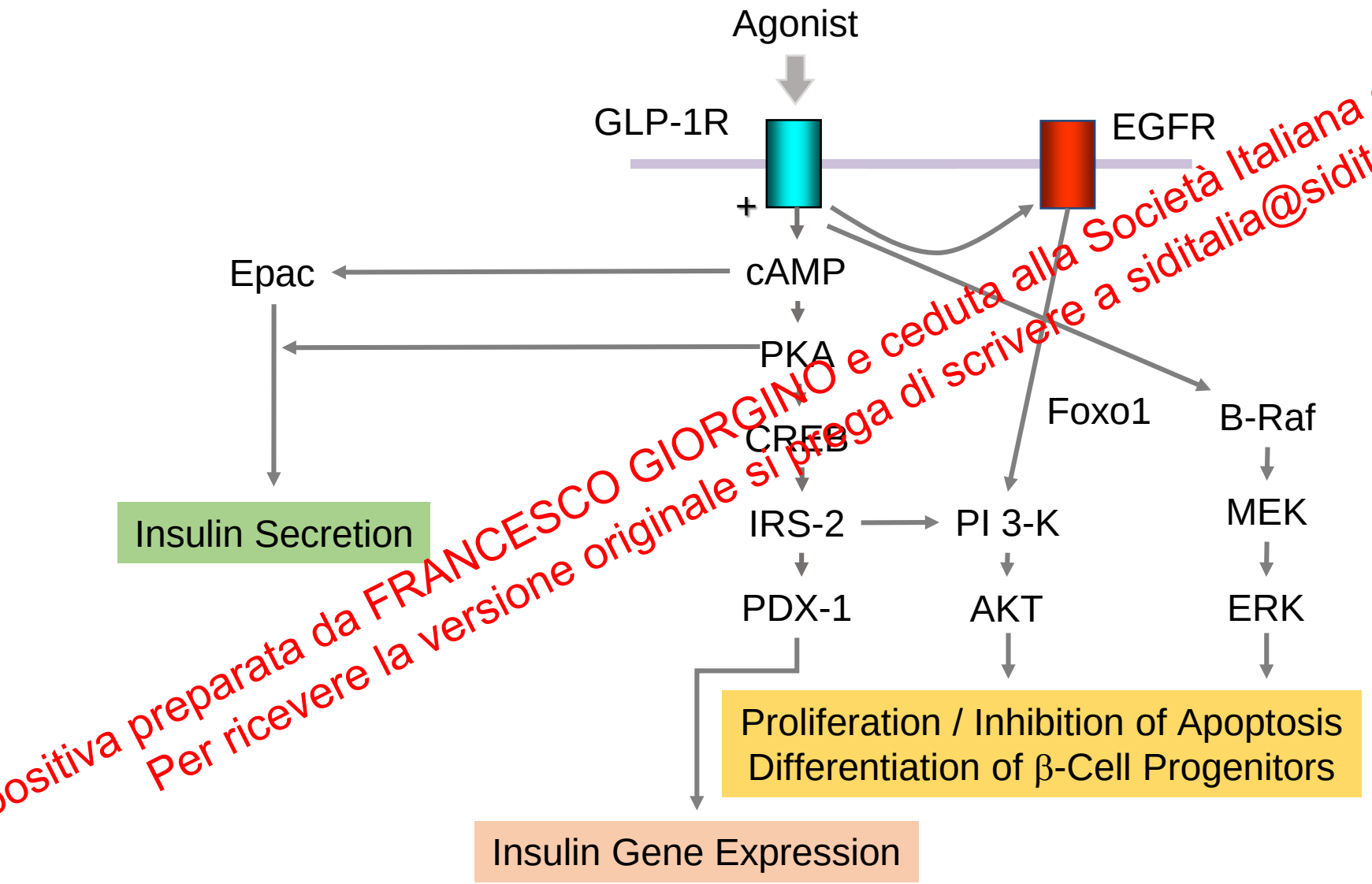
Multiple Forms of GLP-1 Are Secreted *in vivo*

- Multiple forms of GLP-1 are secreted *in vivo*, including GLP-1(1-37) and GLP-1(1-36)NH_2, which are thought to be inactive, and GLP-1(7-37) and GLP-1(7-36)NH_2, which are biologically active.

- GLP-1(7-37) and GLP-1(7-36)NH_2 are produced from their full-length precursors by the action of prohormone convertase (PC)1/3 and appear to be equipotent in their ability to stimulate insulin secretion.

- In humans, the majority of GLP-1 in the circulation is GLP-1(7-36)NH_2.

GLP-1 Signaling in Beta-Cells



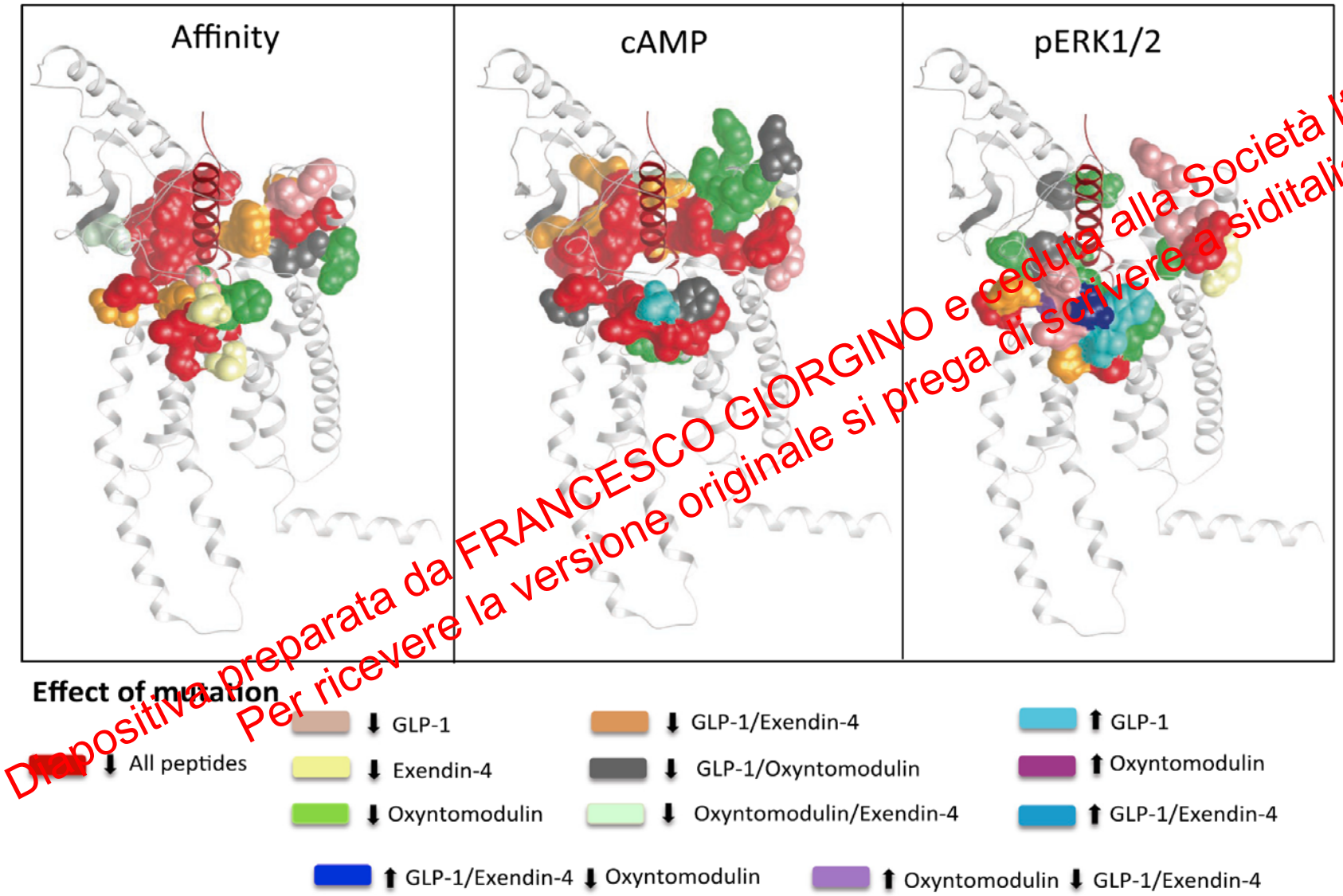
Giorgino F et al, *Diabetes Res Clin Pract* 74: S152–5, 2006; Natalicchio A et al, *Endocrinology* 157:2243-58, 2016

Differentiation of GLP-1 RAs: Glycemic Targets and Mechanisms of Action

Parameters	Short-acting (Prandial) GLP-1 receptor agonists	Long-acting GLP-1 receptor agonists
Compounds	Exenatide (twice daily) Lixisenatide (once daily)	Liraglutide (once daily) Albiglutide (once weekly) Dulaglutide (once weekly) Exenatide LAR (once weekly)
Half-life	2–5 hours	12 hours – several days
Receptor activation	Intermittent	Continuous
Effects		
• Fasting glucose reduction	Modest	Strong
• Fasting insulin secretion	No effect	Stimulation
• Fasting glucagon secretion	Mild reduction	Strong reduction
• Postprandial glucose excursion	Strong reduction	Modest reduction
• Postprandial glucagon secretion	Strong reduction	Mild reduction (?)
• Postprandial insulin secretion	Reduction	Stimulation
• Gastric emptying	Strong deceleration	Mild deceleration
• HbA1c reduction	-0.6–1.2%	-0.9–1.6%

Meier JJ. *Nat Rev Endocrinol* 2012; 8: 728-742
Giorgino F, et al. *Diabetes Metab Res Rev* 2016 [Epub ahead of print]

Amino Acid Residues in the GLP-1 Receptor That Are Important for GLP-1, Oxyntomodulin, and Exendin-4 Binding and Signaling



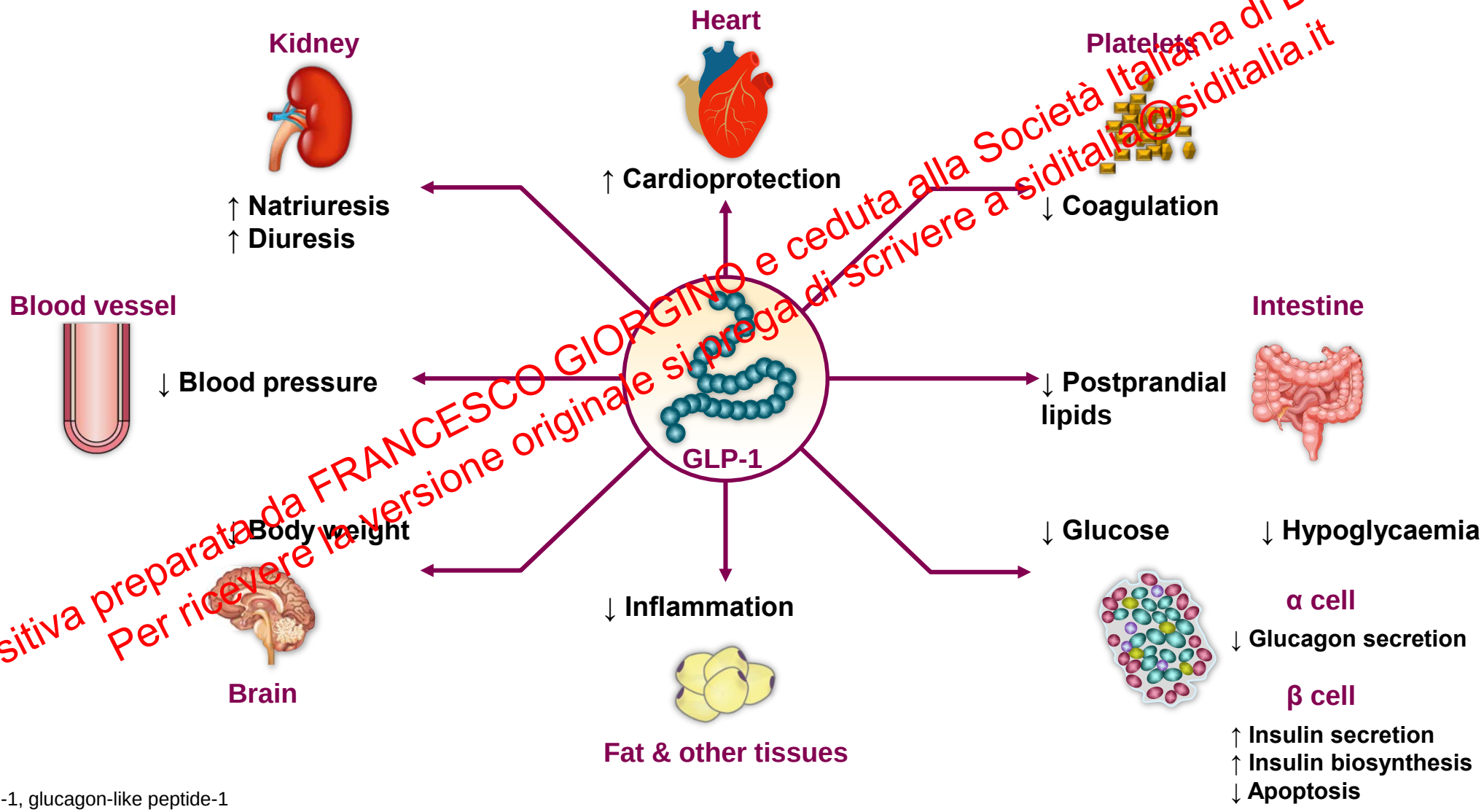
Residues highlighted in red reduce function of all three peptides, those in pink selectively reduce GLP-1 only, those in yellow selectively reduce exendin-4 only, and those in green selectively reduce oxyntomodulin only.

A large number of residues are important for both GLP-1 and exendin but not oxyntomodulin, and these are highlighted in orange.

Other colors represent either enhanced function or existence of opposite effects when mutated on oxyntomodulin compared to GLP-1 and exendin-4.

Wootten et al., *Cell* 2016;165:1632–1643.

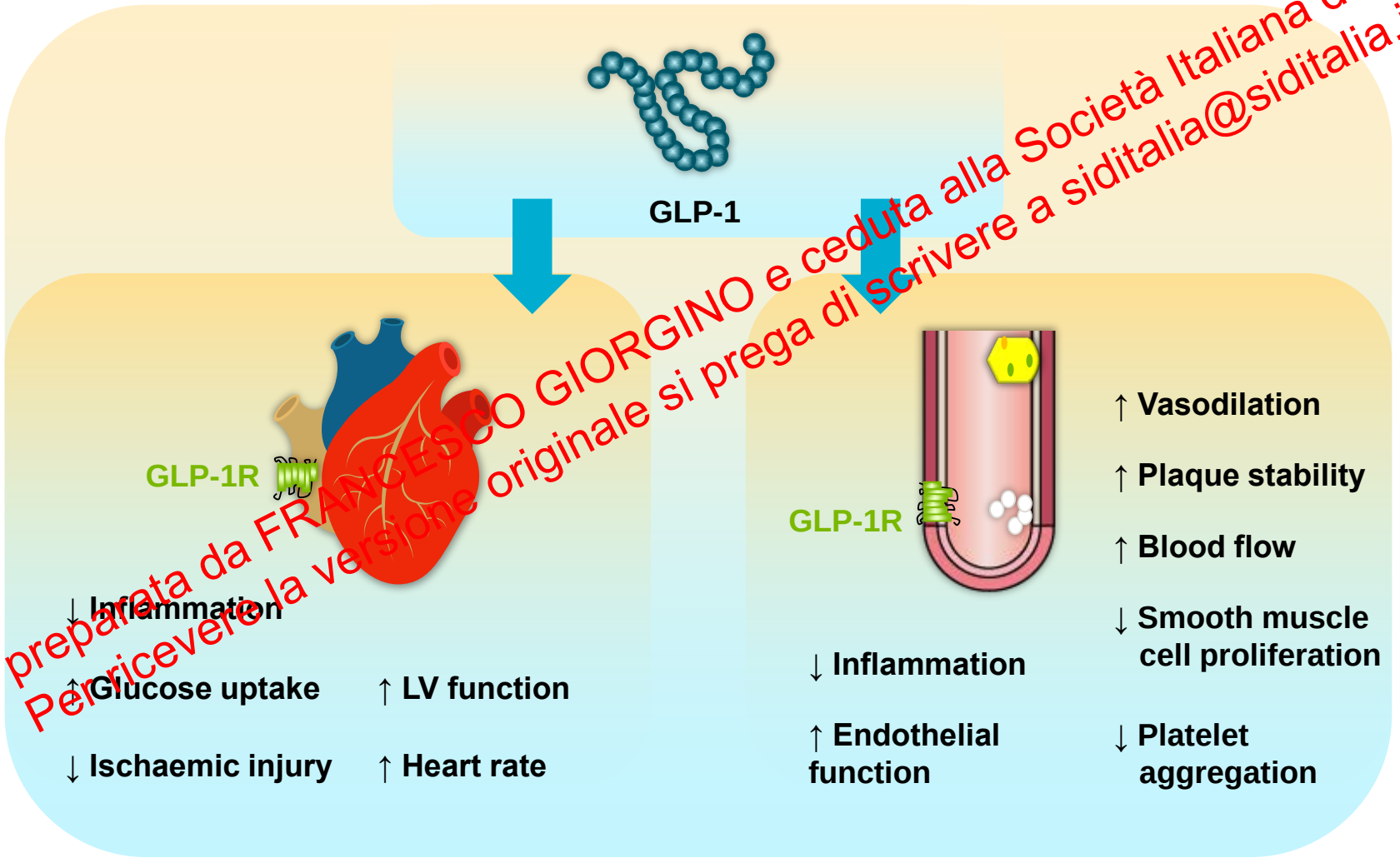
GLP-1 Effects on CV Risk through Direct and Indirect Actions in Multiple Organs



CV, cardiovascular; GLP-1, glucagon-like peptide-1

Drucker DJ. *Cell Metab* 2016;24:15–30

Direct and Indirect Actions of GLP-1 in the Heart and Blood Vessels



CV, cardiovascular; GLP-1, glucagon-like peptide-1

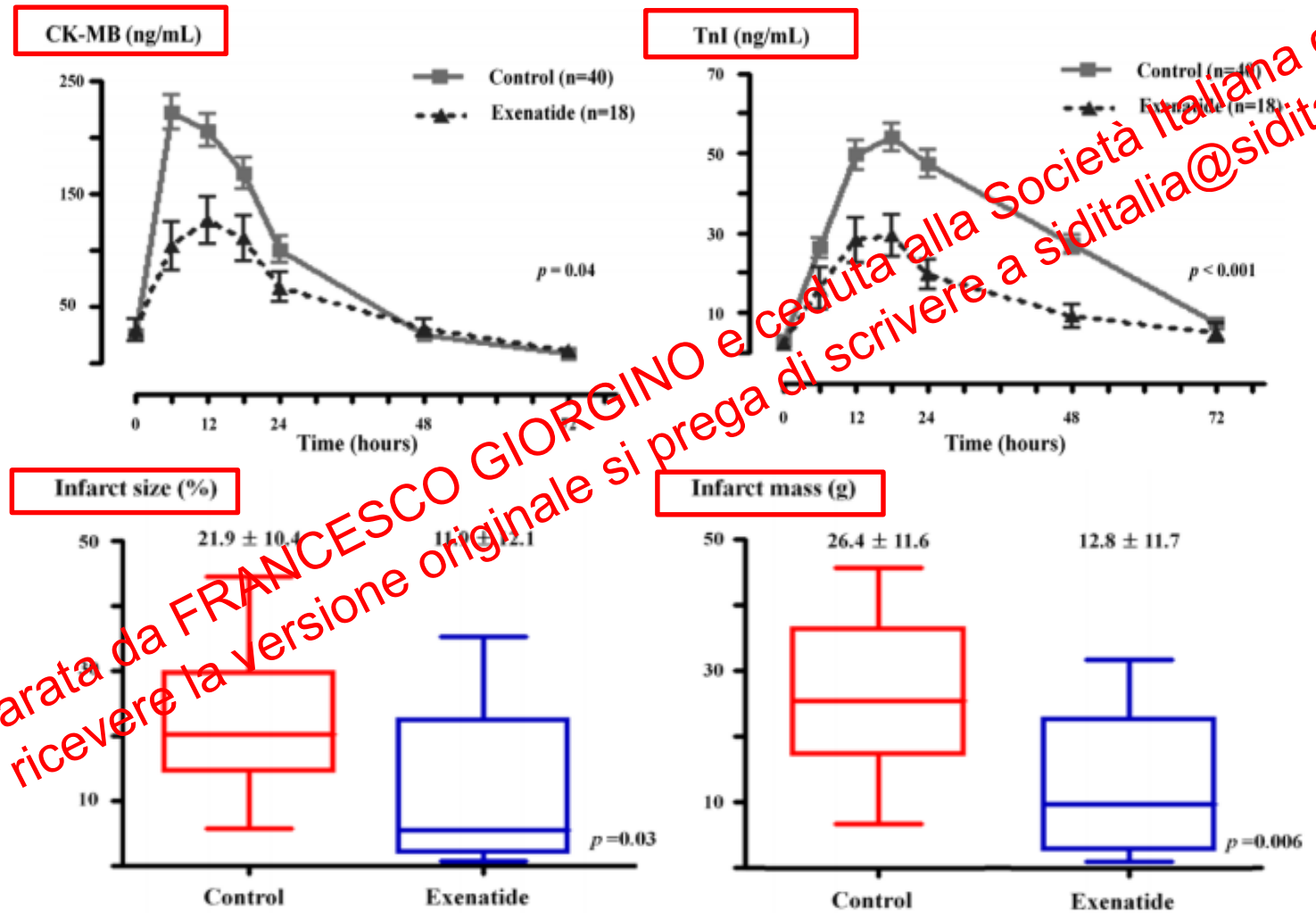
Drucker DJ. *Cell Metab* 2016;24:15–30

Effects of GLP-1 or GLP-1 Receptor Agonists in Human Studies, with Potential Impact on Cardiovascular Function

Effect	GLP-1 [7-36 amide or 7-37]	Liraglutide	Exenatide
Cardioprotection against ischemia	↑ LVEF; ↑ regional wall motility	preserved LVEF after PCI/NSTEMI	↑ salvage index after STEMI; ↓ infarct size

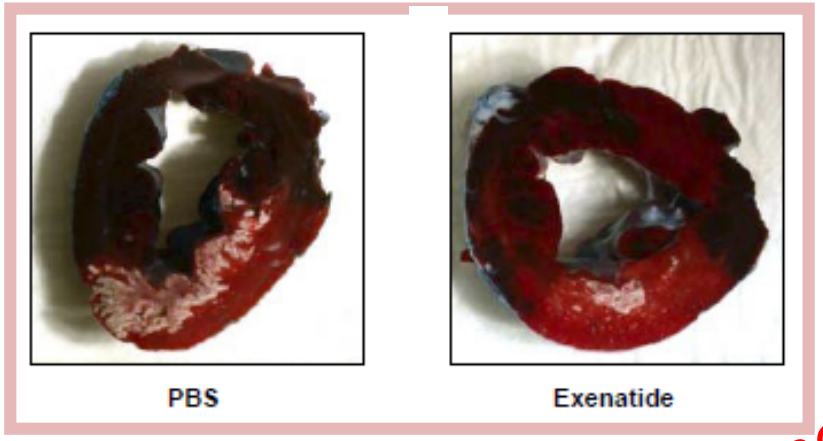
ACh, acethylcholine; CPC, cardiac progenitor cell; EC, endothelial cell; HUVEC, human umbilical vein endothelial cell; IL, interleukin; LVEF, left ventricular ejection fraction; NOS, nitric oxide synthase; NSTEMI, non ST-elevated myocardial infarction; PCI, primary coronary intervention; T2D, type 2 diabetics; TNF, tumour necrosis factor..
Adapted from Nauck MA, et al., *Circulation* 2017;136:849-870

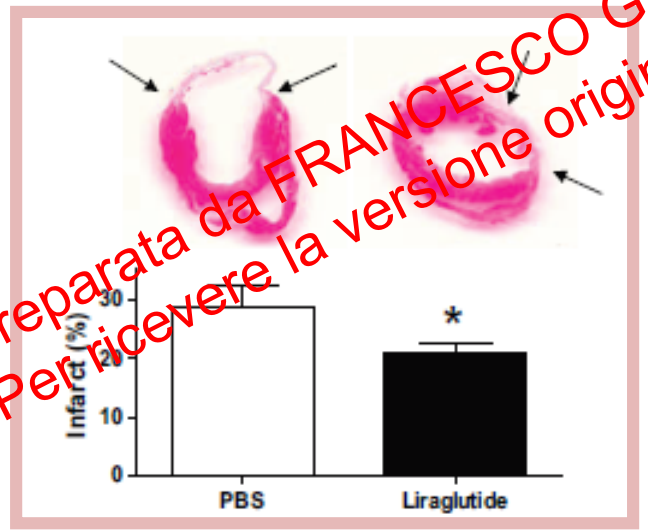
Cardioprotective Effects of Exenatide in Patients With Myocardial Infarction Undergoing Primary PCI

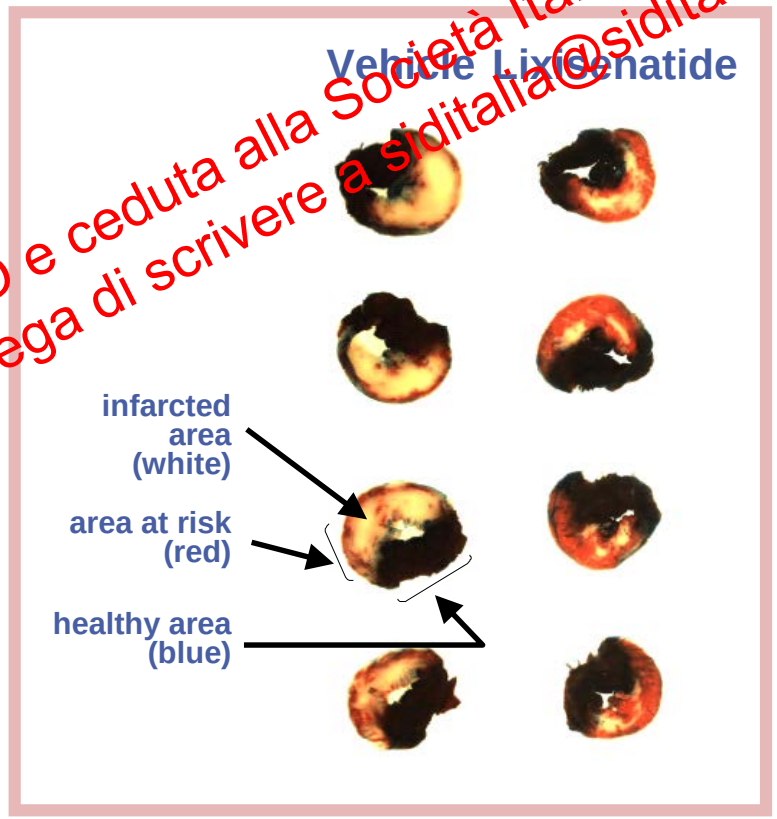


Woo J.S. et al., Arterioscler. Thromb. Vasc. Biol., 2013

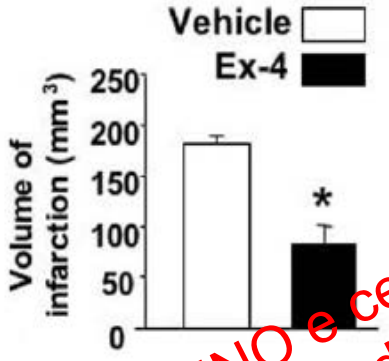
GLP-1 RA and Cardioprotection

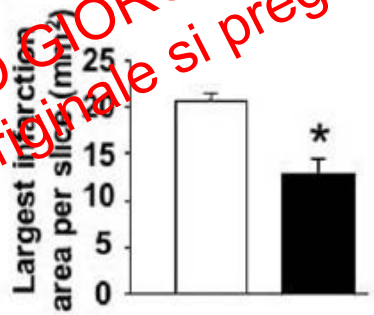


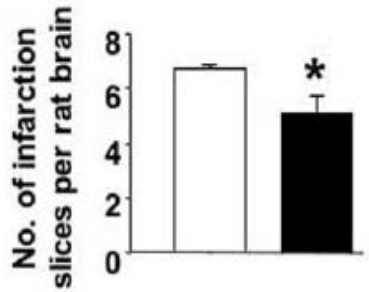


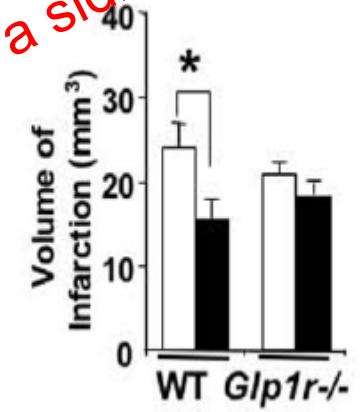


GLP-1 Receptor Stimulation Preserves Primary Cortical Neurons in Rodent Models of Stroke





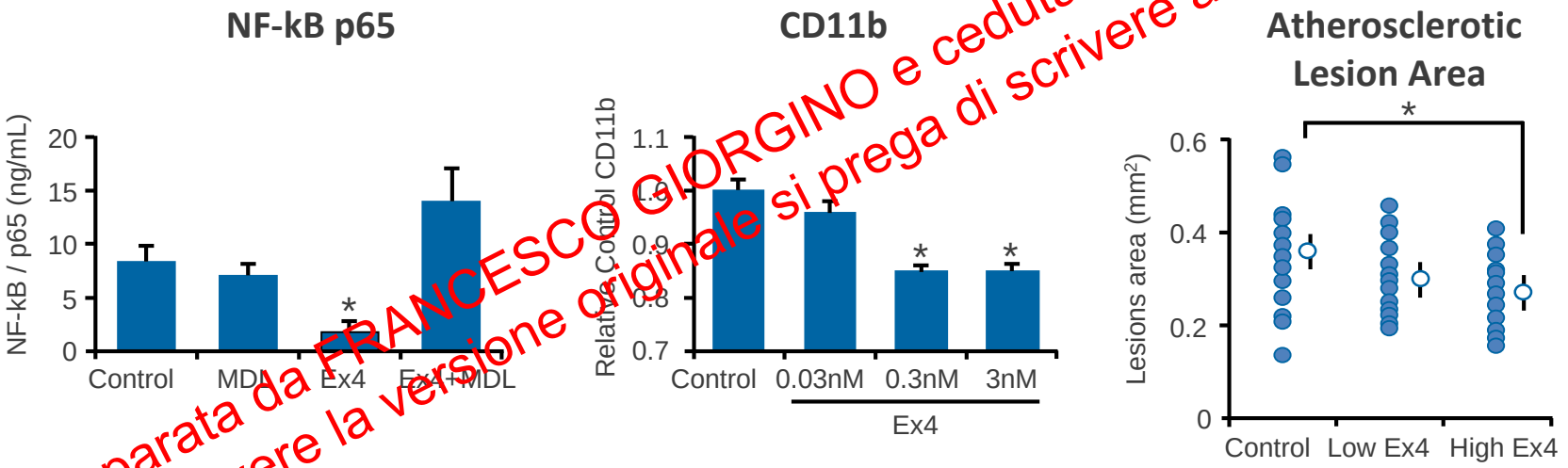




Li Y, PNAS, 2009

GLP-1 Mimetic Decreases Inflammatory Signaling and Atherosclerotic Lesion Area in a Murine Model

Treatment with Exendin-4 decreased inflammatory and adhesion molecules on monocytes and macrophages and reduced atherosclerotic lesional area



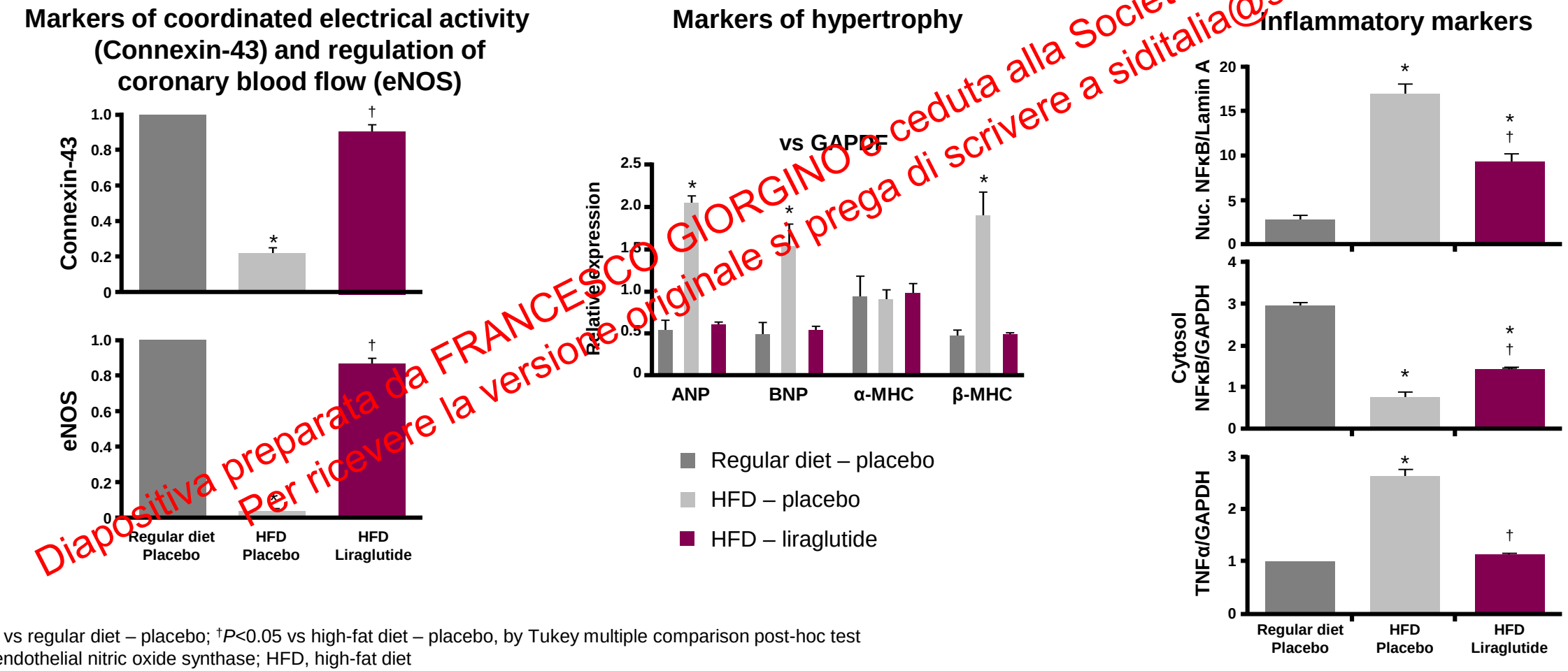
*P<0.05 vs. control

CD11b, monocyte adhesion molecule; Ex4, exendin-4; MDL, MDL-12330A (a cAMP inhibitor); NF-kB, Nuclear factor kappa B.

Arakawa M et al. *Diabetes.* 2010;59:1030-1037

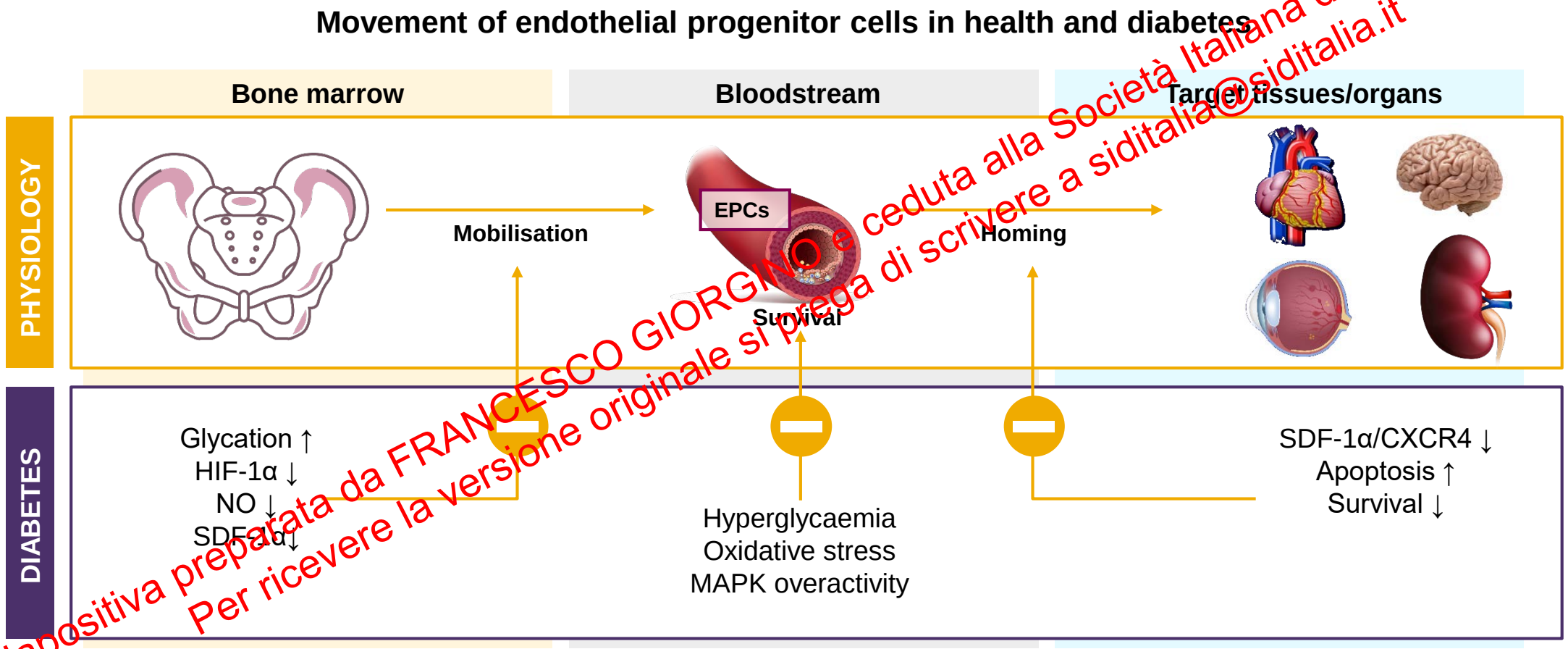
Liraglutide Reduced Obesity-induced Perturbations in Cardiac Endothelial NO Synthase and Markers of Hypertrophy and Inflammation

- Effect of 1-week treatment with liraglutide (30 µg/kg) in mice fed on 45% high-fat diet



*P<0.05 vs regular diet – placebo; †P<0.05 vs high-fat diet – placebo, by Tukey multiple comparison post-hoc test
eNOS, endothelial nitric oxide synthase; HFD, high-fat diet
Noyan-Ashraf MH, et al. *Circulation* 2013;127:74–85

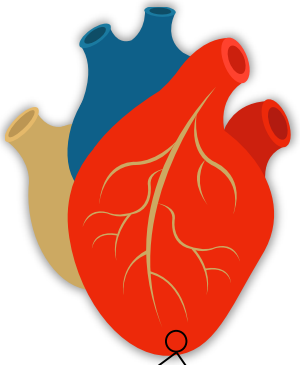
Atherosclerosis is Associated with Reduced Levels or Dysfunction of Circulating Endothelial Progenitor Cells (EPCs)



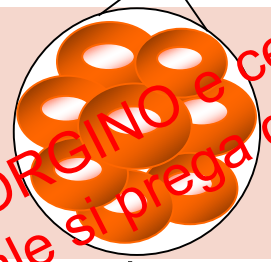
AGE, advanced glycation end-product; CRP, C-reactive protein; EPC, endothelial progenitor cell; FFA, free fatty acid; HIF-1α, hypoxia-inducible factor-1α; MAPK, mitogen-activated protein kinase; PAI-1, plasminogen activator inhibitor-1; ROS, reactive oxygen species; SDF-1α, stromal cell-derived factor-1α; TG, triglyceride; TNFα, tumour necrosis factor α; VLDL, very low-density lipoprotein

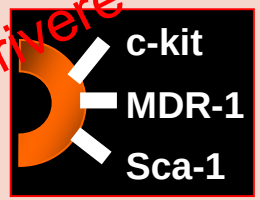
Sena CM, et al. *Biochim Biophys Acta* 2013;1832:2216–2231

The Heart is a Self-renewing Organ

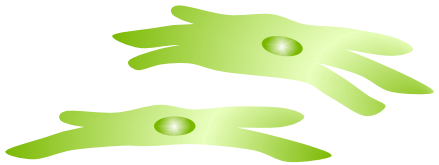


Cardiac stem cells

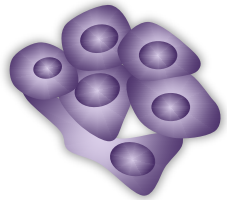




Endothelial cell



Cardiomyocyte

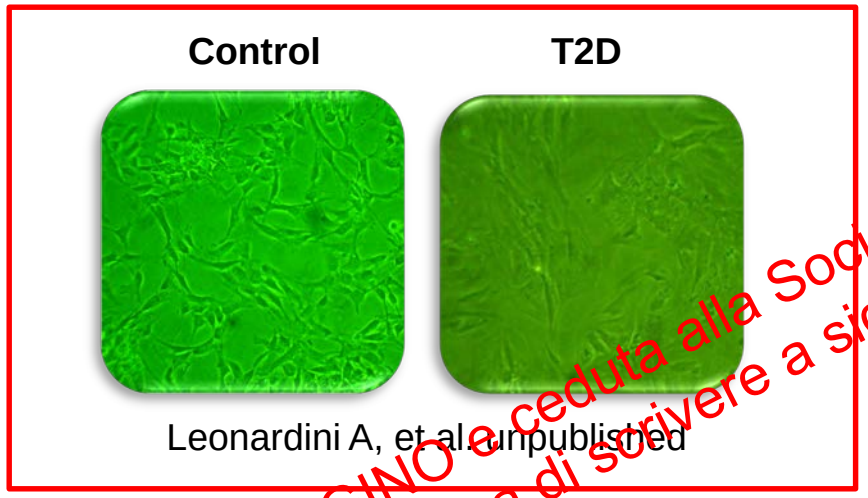


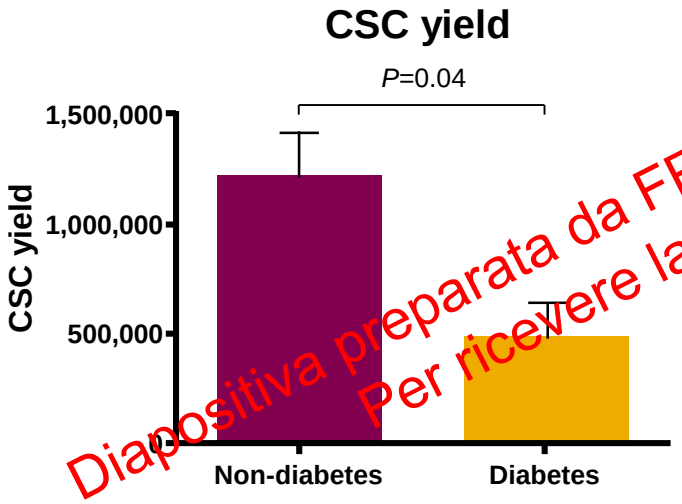
Smooth muscle cell

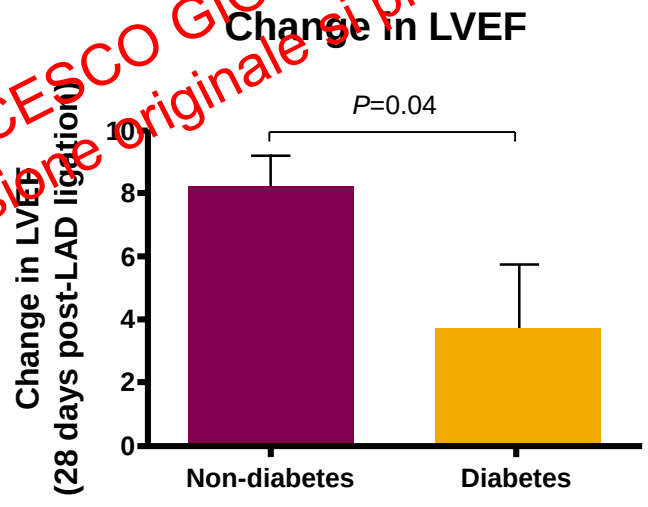
Cardiac disease = cardiac stem cell compartment disease?

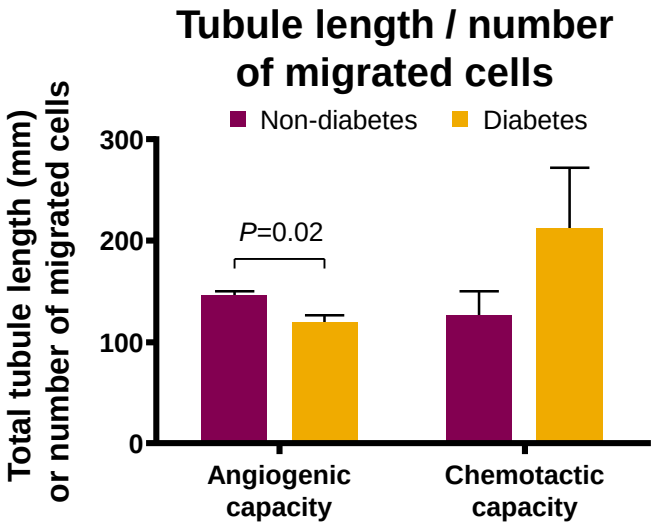
Figure adapted from Anversa P, et al. *Circulation* 2006;113:1451–1463

Diabetes Mellitus Impairs Human Cardiac Stem Cell Function





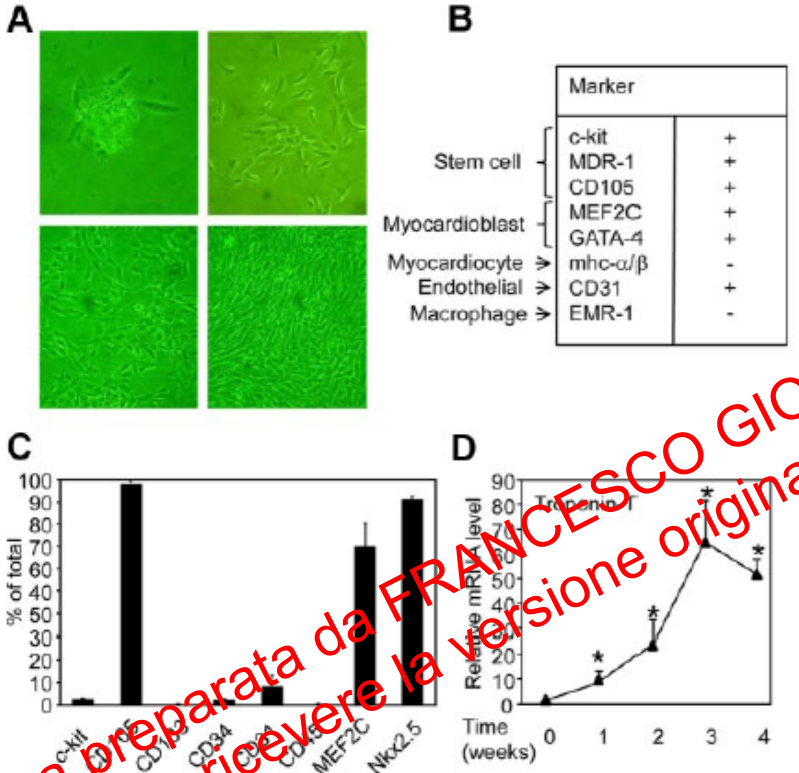




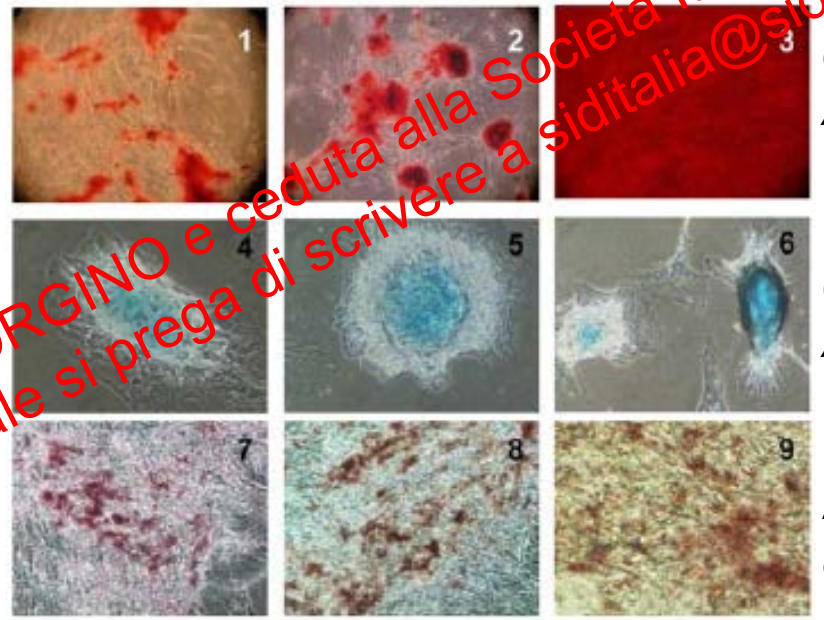
CSC, cardiac stem cell; LAD, left anterior descending; LVEF, left ventricular ejection fraction
Molgat AS, et al. *Circulation* 2014;130:S70–S76

Isolation and Characterization of Human CPC

Phenotypic Profile of Human CPC



Multilineage Differentiation Potential of Human CPC



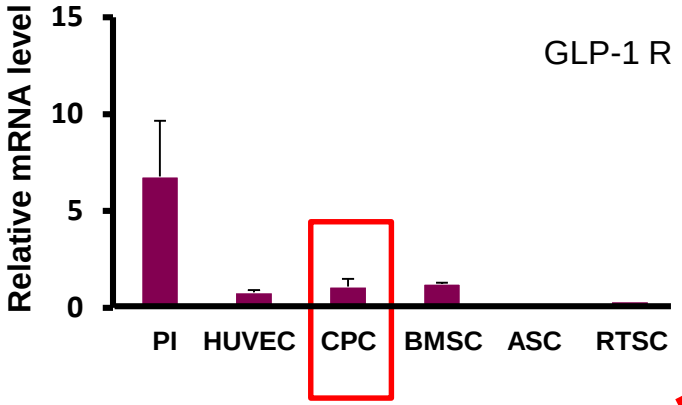
Osteoblast
Alizarin Red

Chondroblast
Alcian Blue

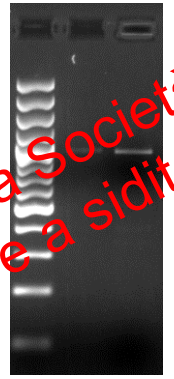
Adipocyte
Oil Red O

Laviola L. et al, Endocrinology, 2012

The GLP-1 Receptor in Human CPC

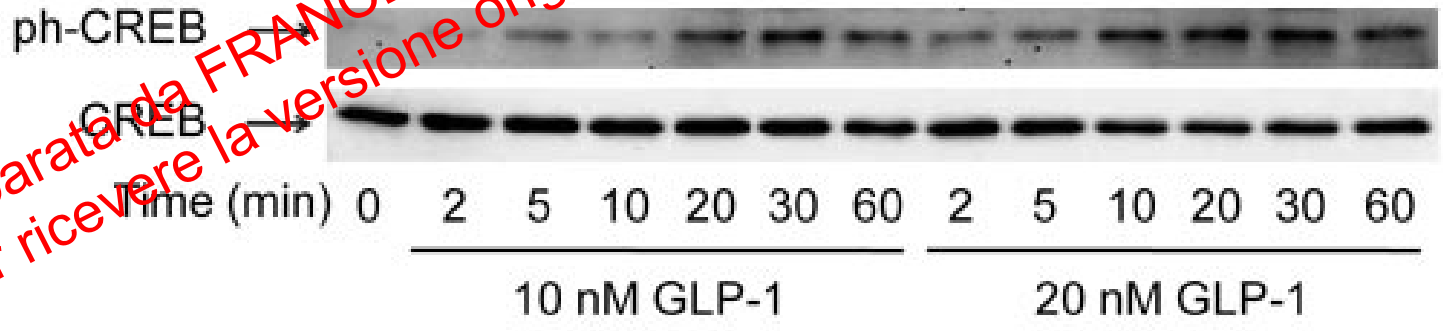


GLP-1 R



GLP-1 R

1. Marker
2. CPC
3. Heart



ASC, adipose tissue-derived stem cells; BMSC, human bone marrow stem cells; CPC, cardiac progenitor cells; CREB, cAMP-response-element binding protein; GLP-1, glucagon-like peptide-1; HUVEC, human umbilical vein endothelial cells; RTSC, human renal tubular stem cells

Laviola L, Leonardini A, et al. *Endocrinology* 2012;153:5770–5781

Mechanisms of Lipotoxicity in the Heart

Diabetes and/or obesity

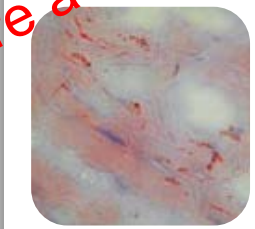
↓

Increased FA delivery

Heart failure

↓

Impaired FA oxidation



Intramyocardial lipid overload (oil-red-O stain for triglycerides)

Altered gene expression | **Ceramide** | **DAG** | **ROS** | **Stress kinases activation**

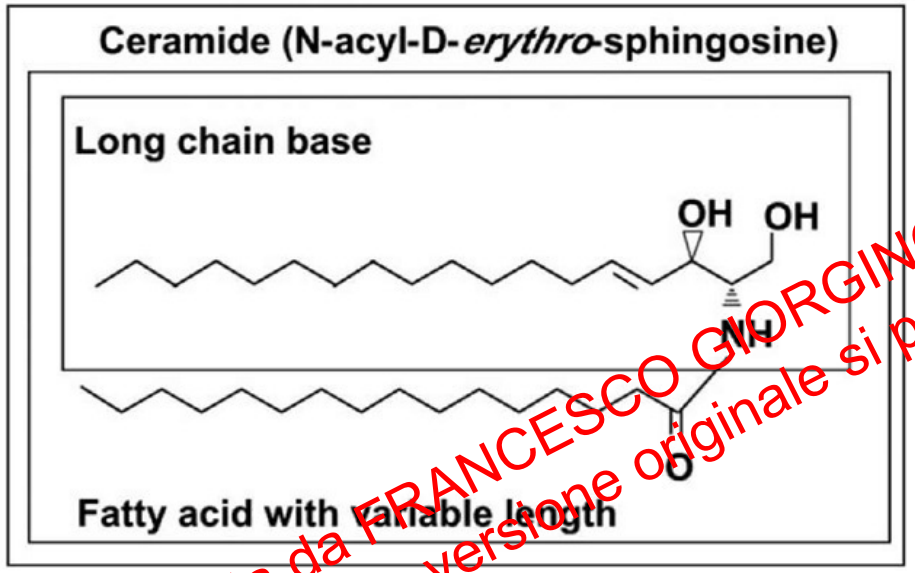
↓

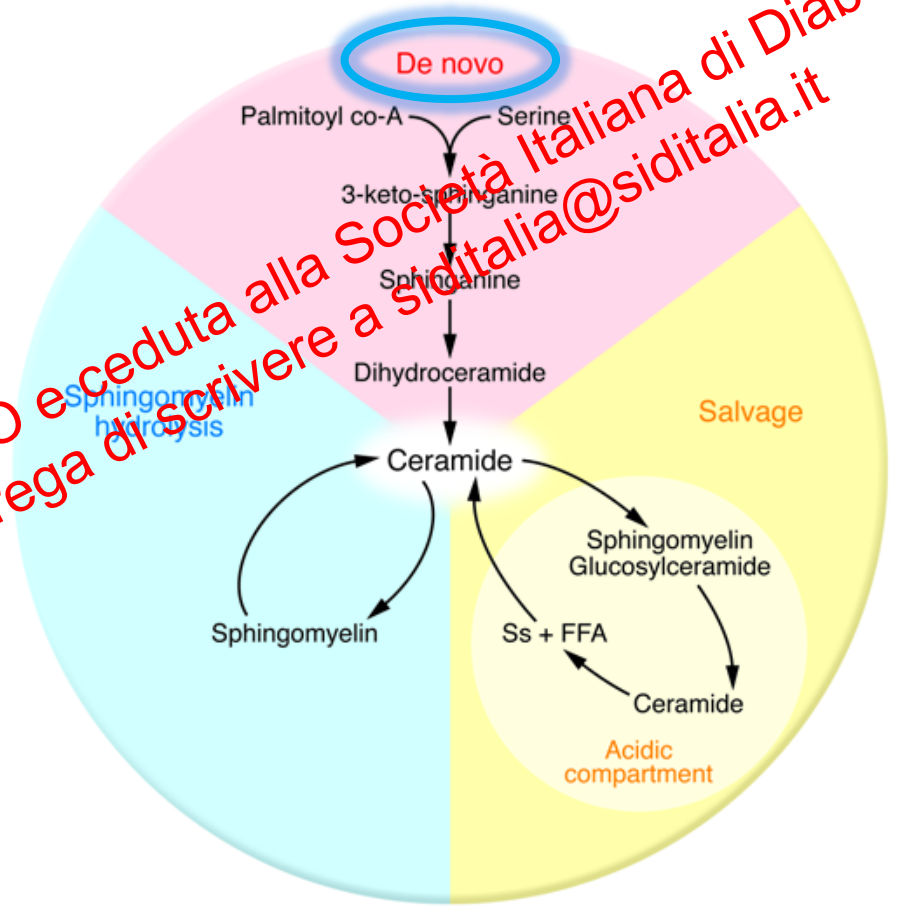
↑ Apoptosis | **↑ Autophagy** | **↑ Senescence** | **Contractile dysfunction**

DAG, diacylglycerol; FA, fatty acid; ROS, reactive oxygen species

Taegtmeyer H, Dilsizian V. *Nat Clin Pract Cardiovasc Med* 2008;5 Suppl 2:S42–S48

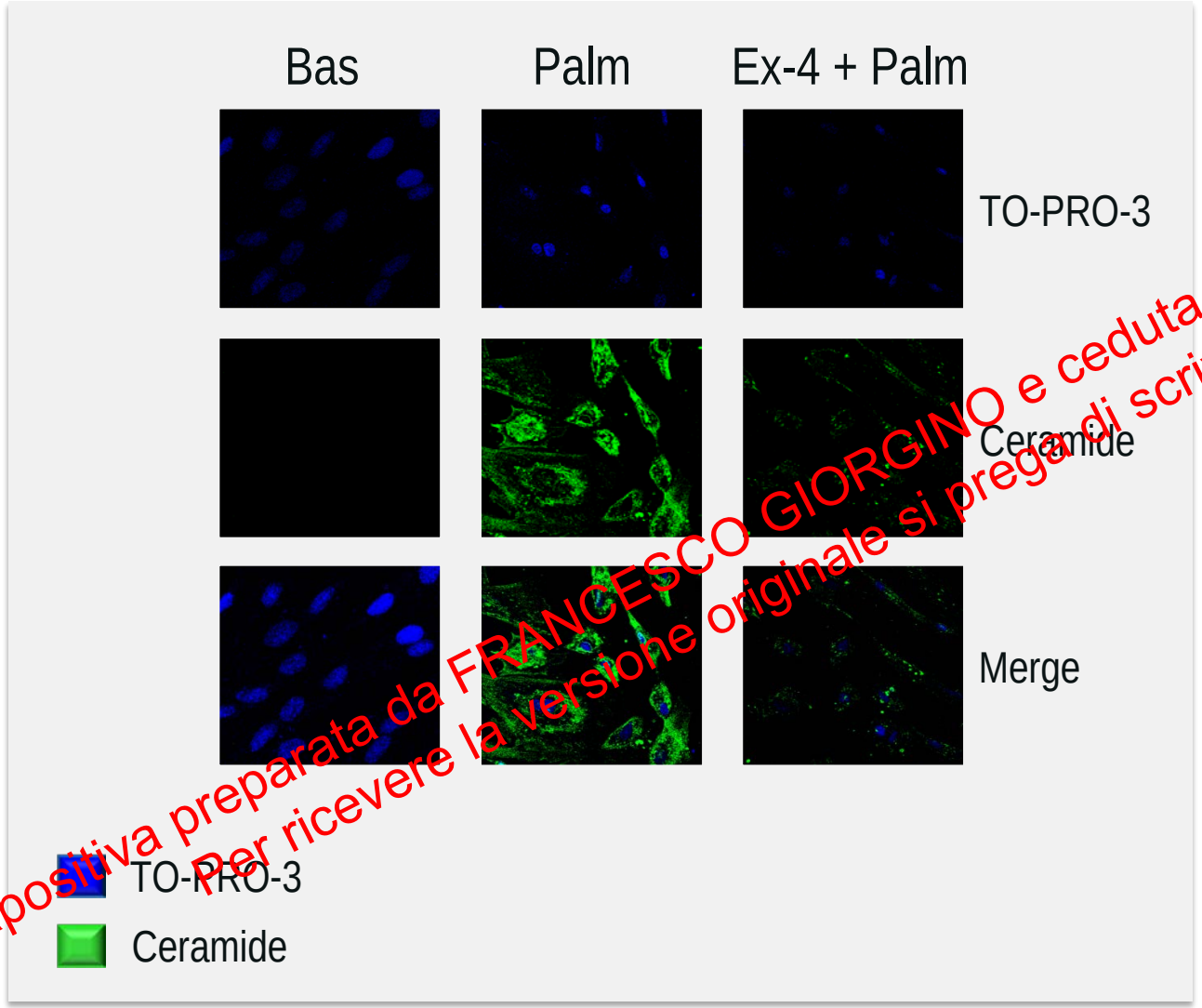
Ceramide Production

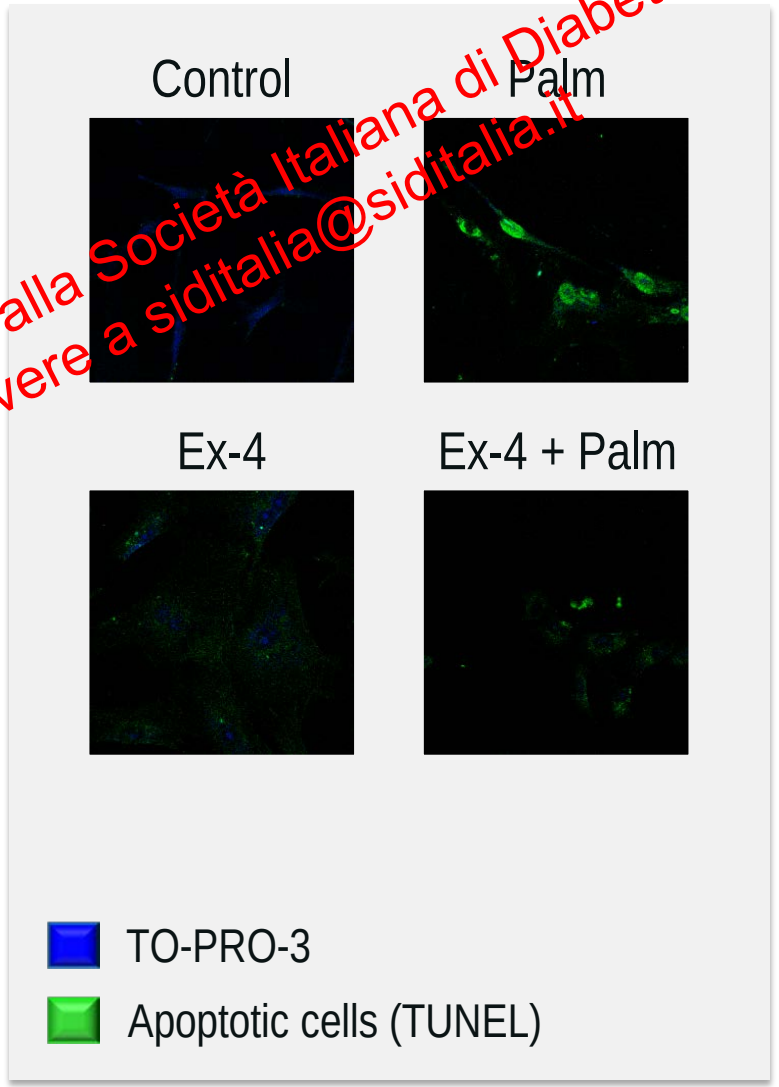




Bickman B. et al., J Clin Invest., 2011

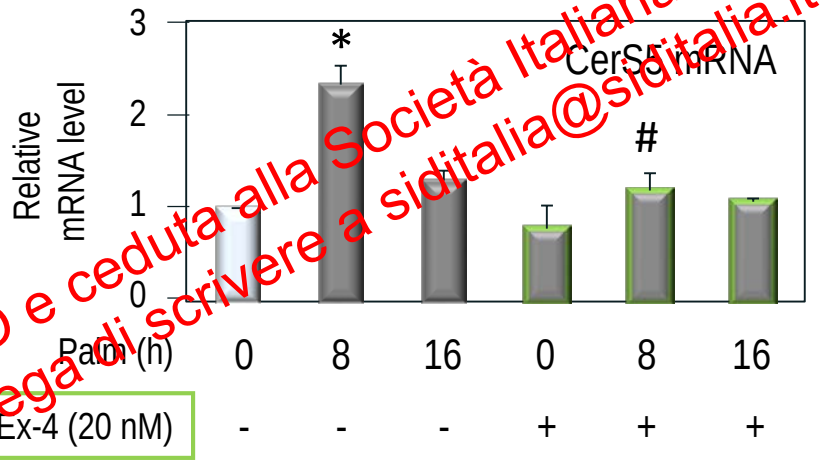
Exendin-4 Inhibits *de Novo* Production of Ceramide and Apoptosis in Human Cardiac Progenitor Cells

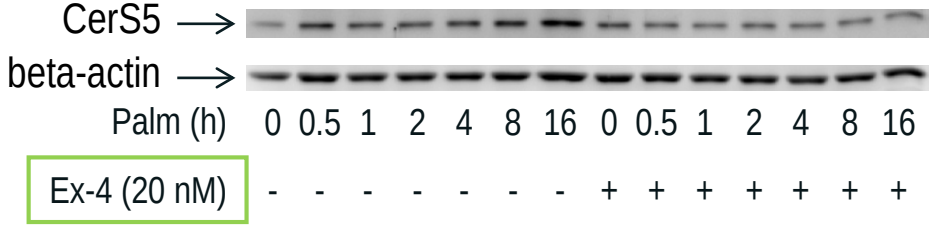




Leondardini A, D'Oria R et al. *JCEM* 2017

Exendin-4 Prevents Induction of Ceramide-Synthase 5 (CerS5) in Human Cardiac Progenitor Cells

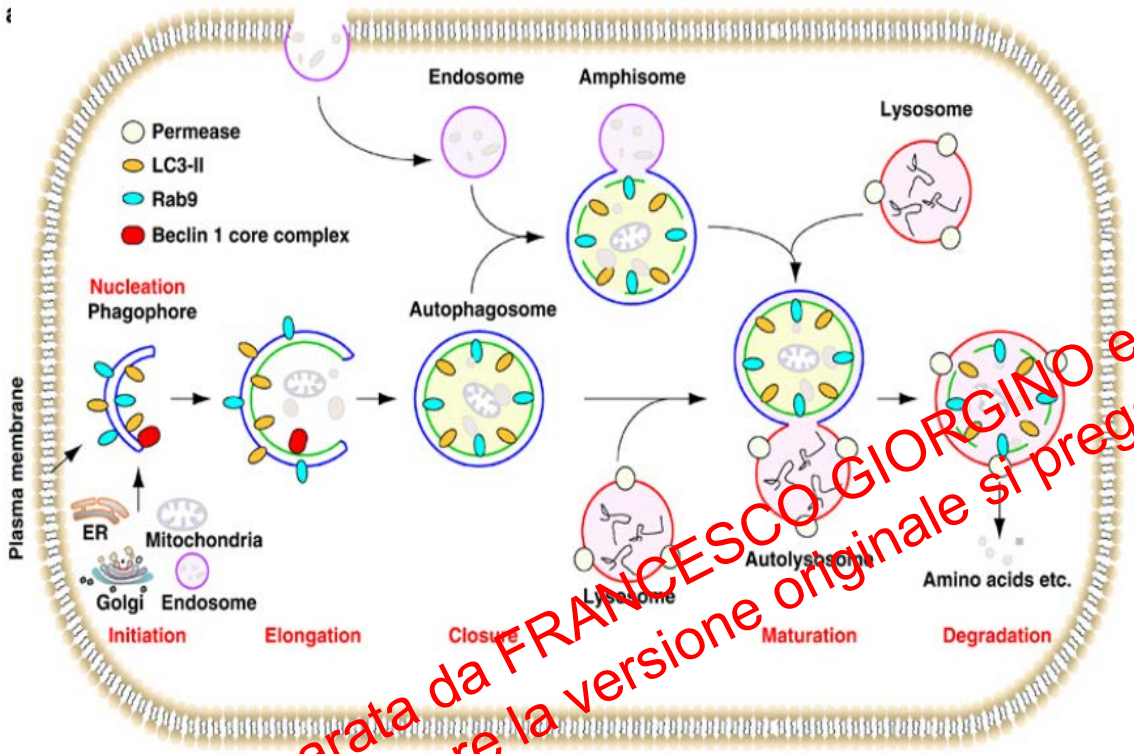


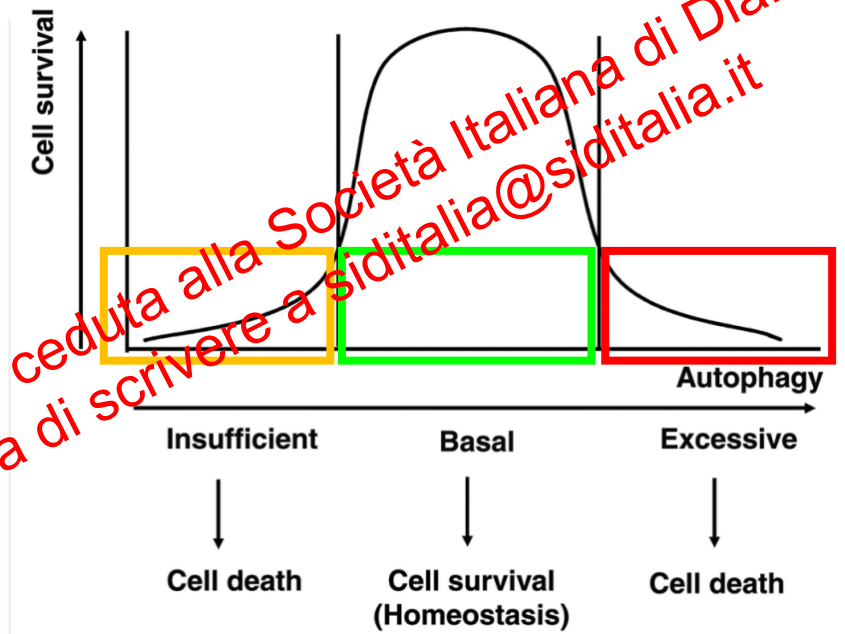


* p < 0.05 Palm vs basal
# p < 0.05 Ex-4+Palm vs Palm

Leondardini A, D'Oria R et al. *JCEM* 2017

Role of Autophagy in Cell Survival

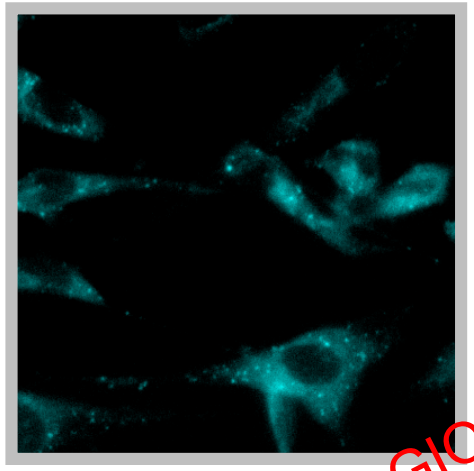




Adapted from Nishida K. et al., Circ Res. 2008

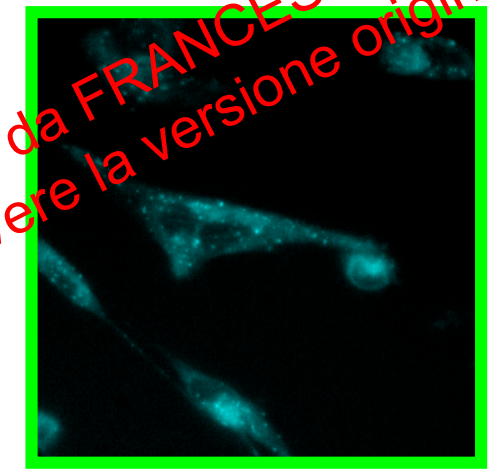
Exendin-4 Prevents Palmitate-Induced Autophagosome Formation

Monodansylcadaverine Staining

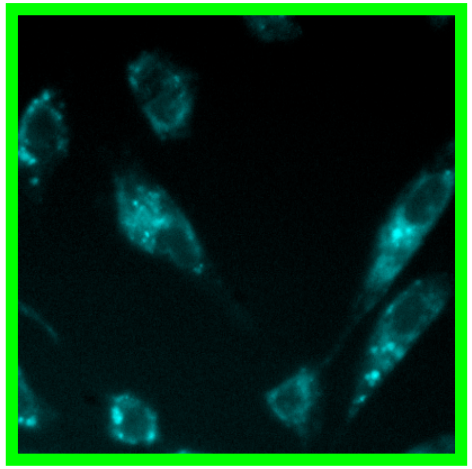


BASAL

PALMITATE

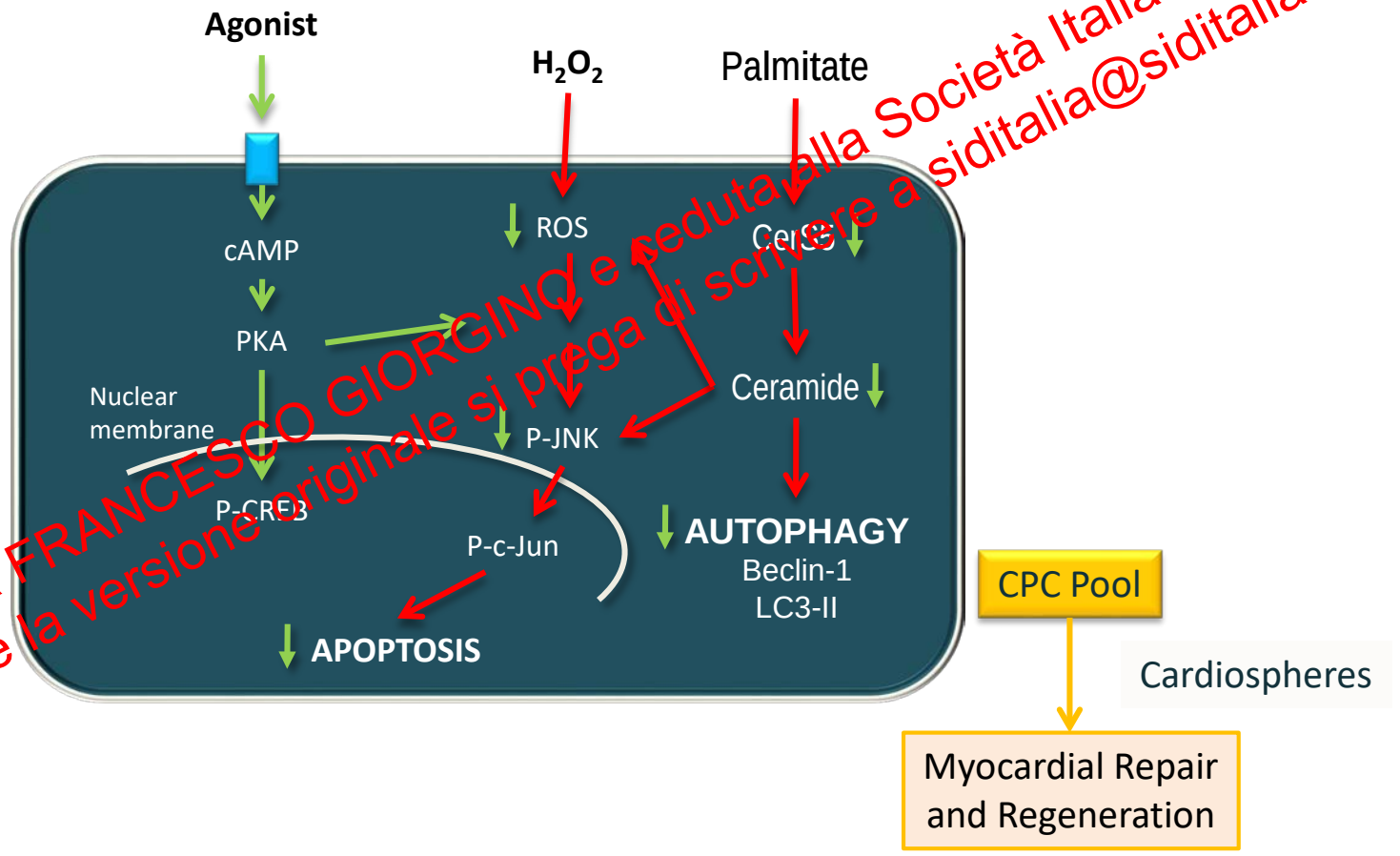


EXENDIN-4



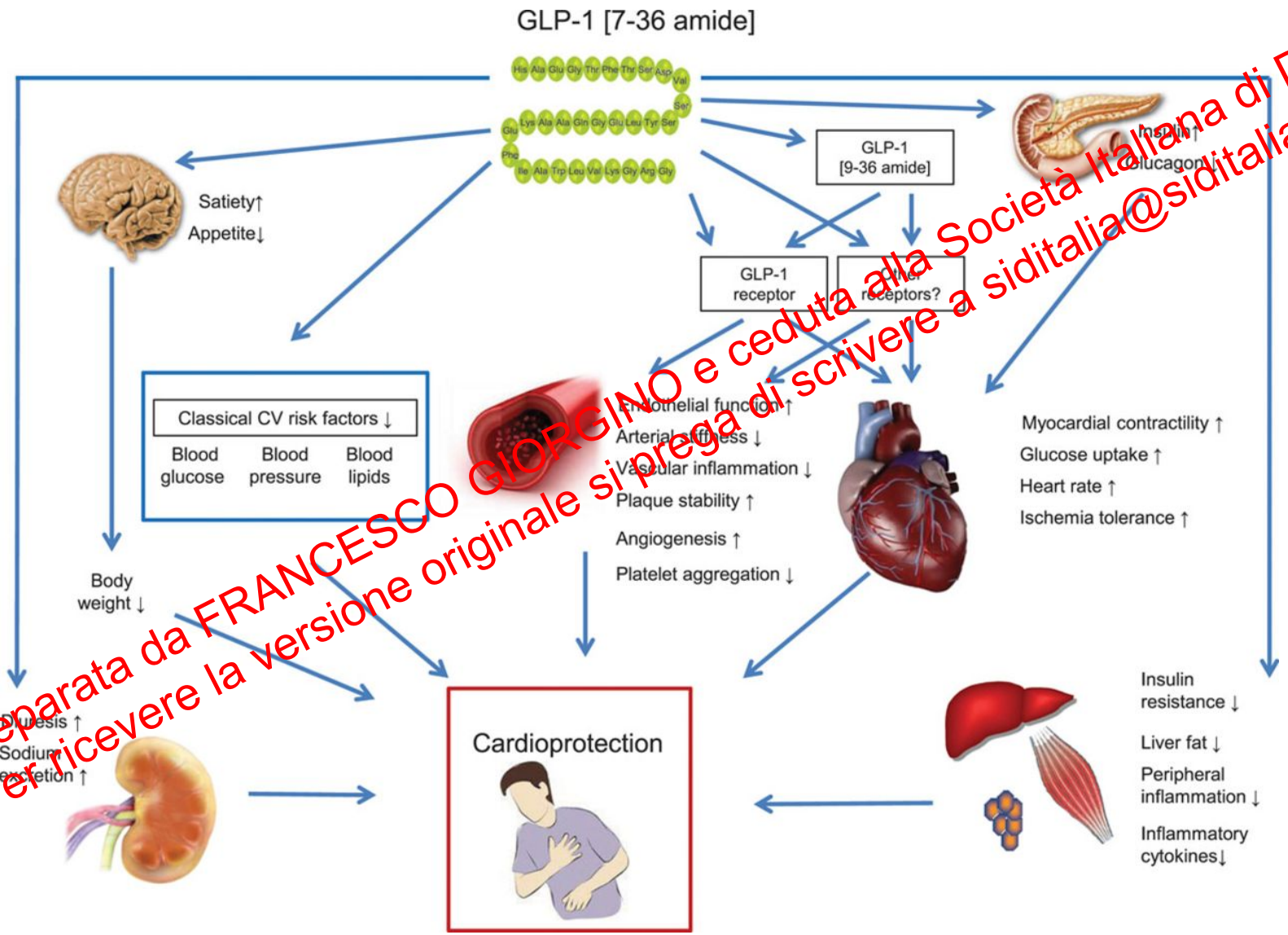
EXENDIN-4 + PALMITATE

GLP-1R Activation Increases Human Cardiac Progenitor Cell (CPC) Survival



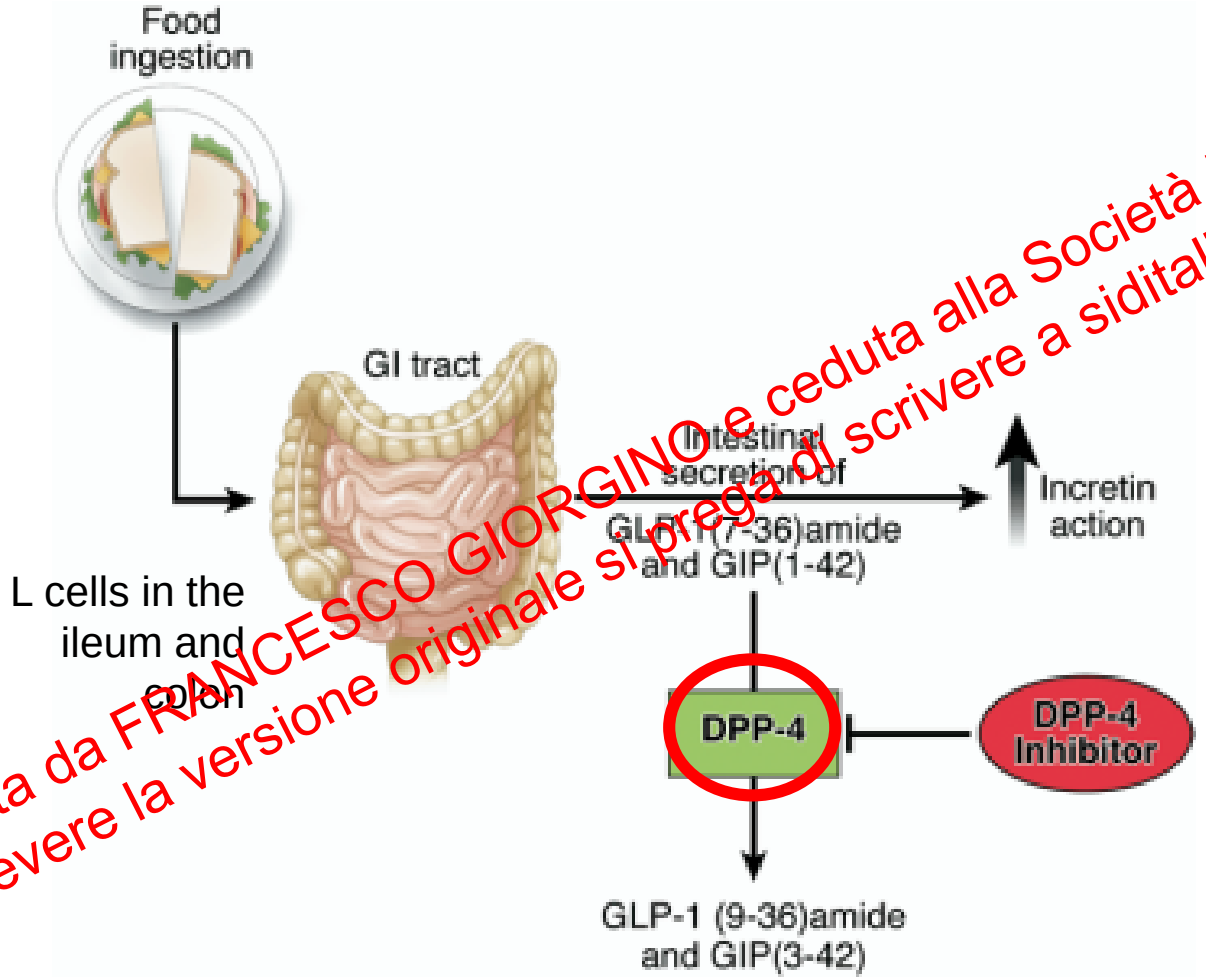
Laviola L., Leonardini A., et al. *Endocrinology* 2012.
Leonardini A., D'Oria R., et al., *JCEM* 2017.
D'Oria R., et al., in preparation.

Mechanisms Mediating a Beneficial Effect of GLP-1R Activation on Cardioprotection



Adapted from Nauck MA, et al., *Circulation* 2017;136:849-870

GLP-1 is Metabolized by the Enzyme DPP-4



GIP, glucose dependent insulinotropic polipeptide; DPP-4, dipeptidyl peptidase-4

Adapted from Baggio et al., Gastroenterolgy, 2007

DPP-4 in the Cardiovascular System

- DPP-4 is widely expressed in most cells and tissues and exhibits enzymatic activity against dozens of chemokines and peptide hormones with roles in inflammation, vascular function, stem cell homing, and cell survival *(Giacco et al., 2015)*.

- DPP-4 exhibits exopeptidase activity through its 2 principal molecular forms, a membrane-tethered 766 amino acid protein with a small intracellular tail and a soluble form that is 39 amino acids smaller, devoid of the short membrane spanning domain and intracellular tail, and yet otherwise structurally identical *(Giacco et al., 2015)*.

- Although soluble DPP-4 exerts vascular, immune, and proinflammatory actions independent of its catalytic activity, the majority of the experimental literature has studied the importance of DPP-4-mediated peptide cleavage in the pathophysiology and treatment of cardiovascular disease.

GLP-1 RA CV Outcomes Trials - Discussion

Selective and potent GLP-1 R activation (vs. DPP-4 inhibition)

Mode of GLP-1 R activation (continuous vs intermittent)

GLP-1 R signaling before, during or after CV event

Direct anti-inflammatory, anti-atherosclerotic, anti-apoptotic/pro-survival effects

Reduction of CV risk factors (HbA1c, weight, BP, lipids, CRP)

Population characteristics (less vs. more advanced CVD)

MACE component being affected