CONGRESSO
SID AMD LAZIO 2015
IL PAZIENTE DIABETICO AL CENTRO:
RICERCA, ASSISTENZA E INNOVAZIONE

La dr.ssa Teresa Mezza dichiara di
**NON** aver ricevuto
negli ultimi due anni
compensi o finanziamenti da
Aziende Farmaceutiche e/o Diagnostiche


HARVARD
MEDICAL SCHOOL


UNIVERSITÀ
CATTOLICA
del Sacro Cuore

# ADATTAMENTO DELLE CELLULE INSULARI ALL'INSULINO-RESISTENZA NELL'UOMO

**TERESA MEZZA, MD**

**CONGRESSO SID AMD REGIONE LAZIO**

**ROMA, 8-9-MAGGIO 2015**

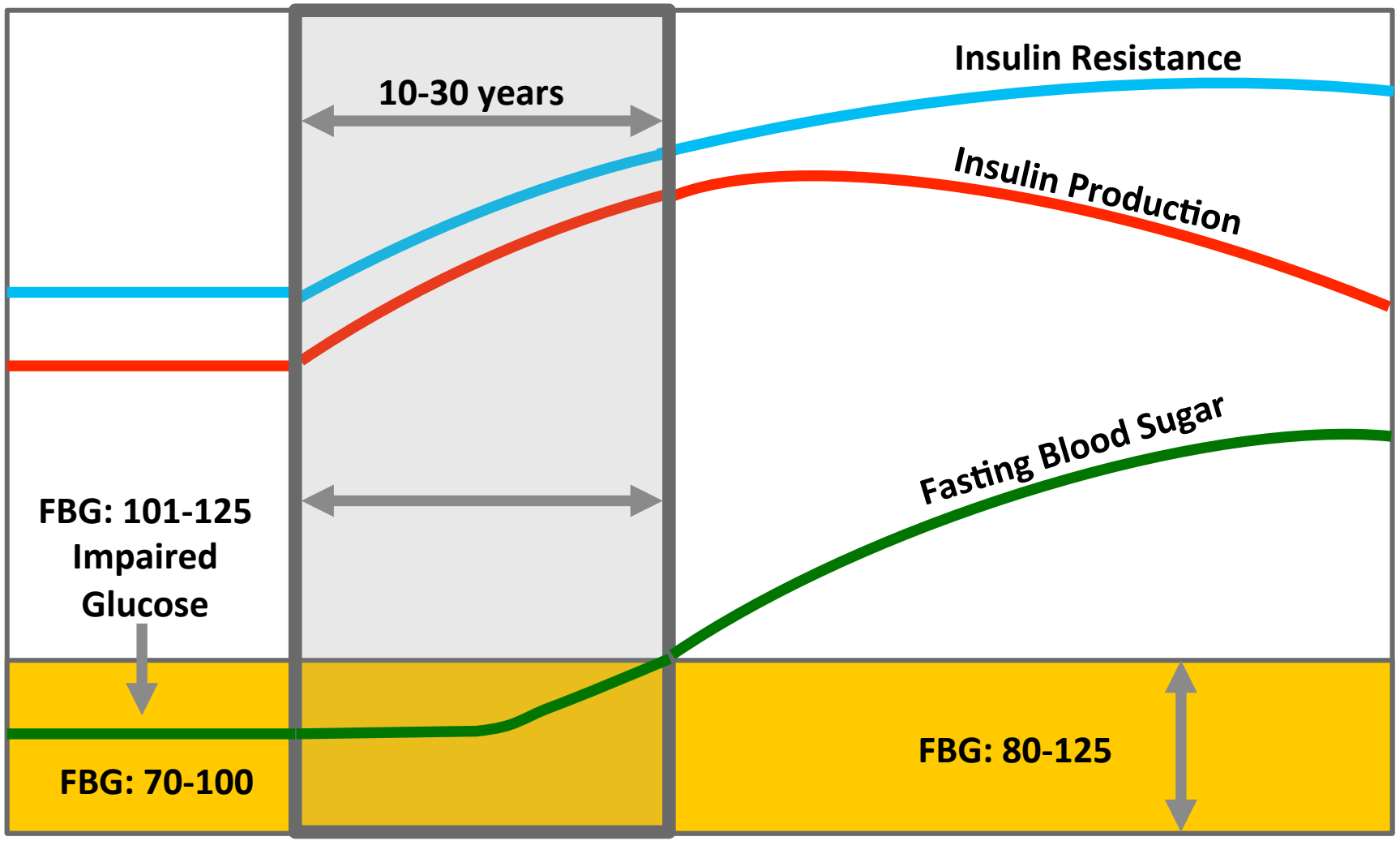
AMD
ASSOCIAZIONE MEDICI DIABETOLOGI
1974
ANNO DI FONDAZIONE

SID
Società Italiana di Diabetologia

# OUTLINE

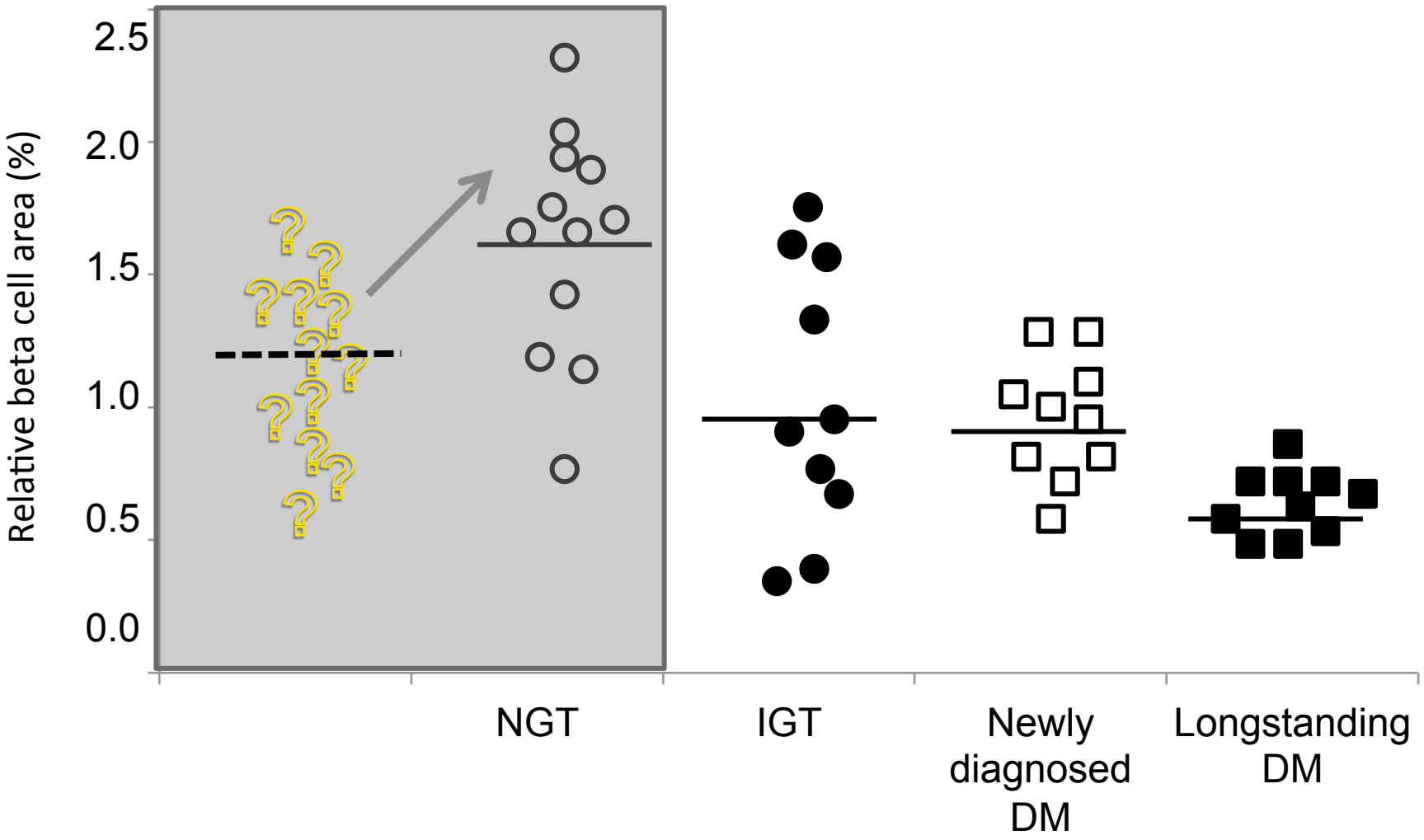
- Background e Ipotesi
- Studio “In Vivo”
- Studi “Ex Vivo”
  - Morfologia insulare
  - Neogenesi
  - Transdifferenziazione
- Modellistica
- Prospettive

# Diabete Mellito Tipo 2: Time course




*Adapted from Type 2 diabetes BASIC 2000 International diabetes center Minneapolis MN*

# DM2 riduce la massa β-cellulare




*Yoneda S. et al.,JCEM , 2013*

## Ipotesi
## Insulin resistenza "*per se*" sia responsabile di alterazione della massa e funzione β cellulare

## Overall Objective

Studiare possibili correlazioni tra un determinato pattern di secrezione e sensibilità insulinica and caratteristiche ex vivo delle cellule insulari.

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# Pazienti e Studio in vivo

Pazienti non diabetici (10 F/8 M, 51±15 aa., BMI 27.9±5.3 kg/m2) sottoposti a duodenocefalopancreasectomia:

Tolleranza Glucidica

*OGTT* (Oral Glucose Tolerance Test; 75 gr glucose)

Insulino sensibilità

Clamp Euglicemico Iperinsulinemica (40mU/$m^2$)

Secrezione insulinica

Clamp *Iperglicemico* (FPG+125 mg/dl + Arginine)

Asse Entero-insulare

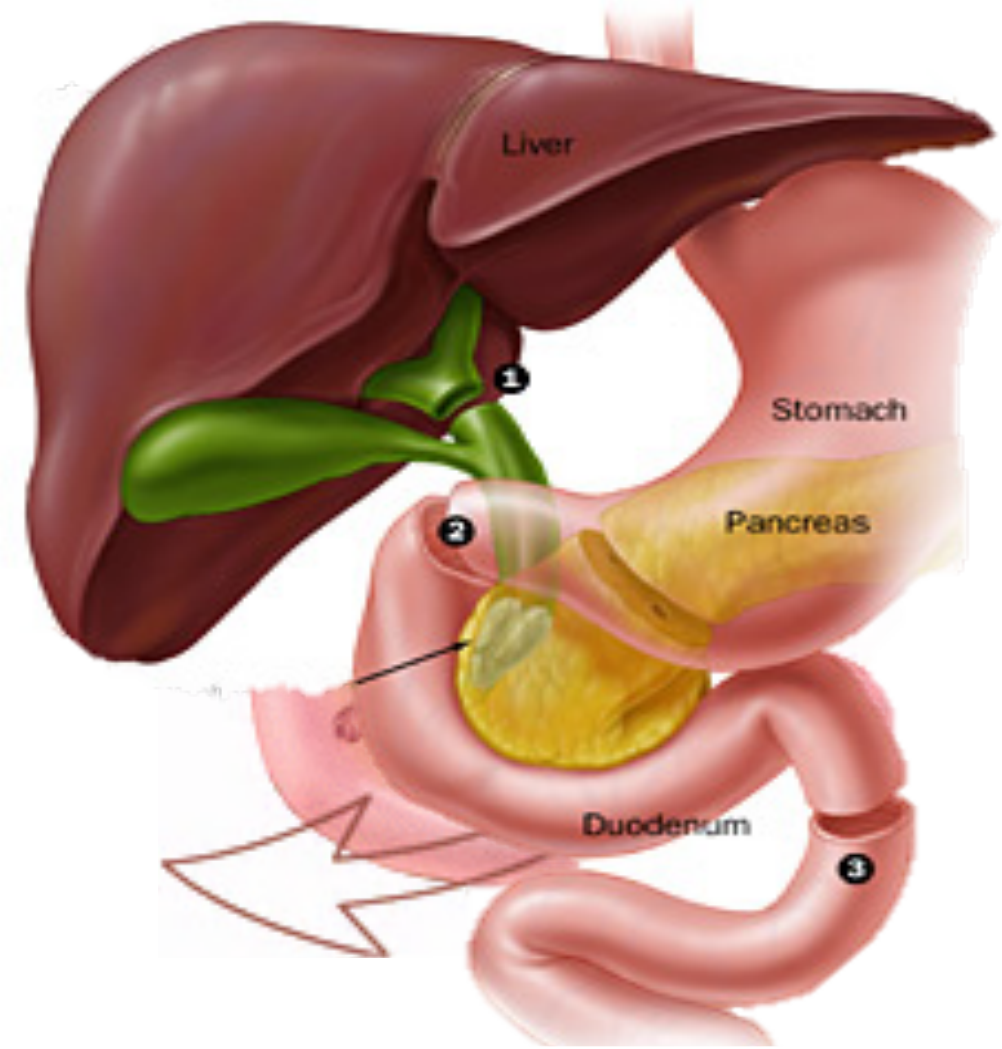
Pasto Misto

# pazienti sottoposti a panx

## divisi per glucose uptake

| | **Insulin sensitive (n. 9)** | **Insulin resistant (n. 9)** |
|---|---|---|
| **Glucose Uptake ($mg \cdot kg^{-1} \cdot min^{-1}$)** | **6.38±0.12** | **3.36±0.34** |
| BMI ($kg/m^2$) | 27.7±3.22 | 28.1±3.7 |
| Waist/hip ratio | 0.93±0.05 | 0.95±0.04 |
| Glucose (mg/dl) | 89.8±11.8 | 90.4±13.7 |
| Insulin (µUI/ml) | 7.83±2.07 | 9.23±4.21 |
| C-peptide (ng/ml) | 2.52±0.44 | 2.7±0.67 |
| Glicose AUC (mg/dl x 120' x $10^3$) | 194±33.7 | 207±31.8 |
| Insulin AUC (µUI/ml x 120' x $10^3$) | 33.9±6.8 | 44.9±16.2 |
| C-peptide AUC (ng/ml x 120' x $10^3$) | 0.9±0.2 | 2.5±0.1 |

# Whipple Surgery



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# Ex vivo data - Pancreas

**Morfologia Insulare**

IHC for glucagon, insulin and somatostatin

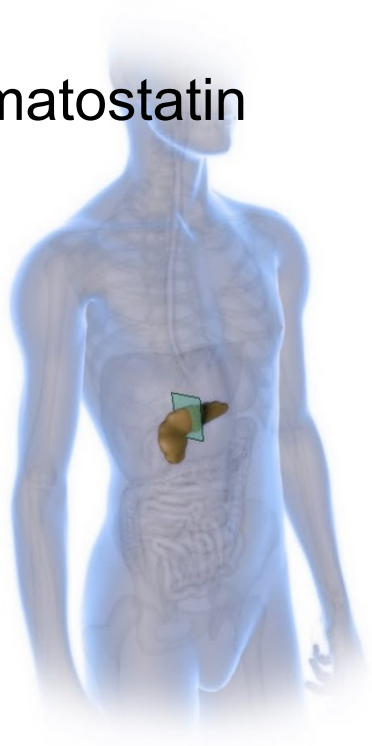
**Neogenesi**

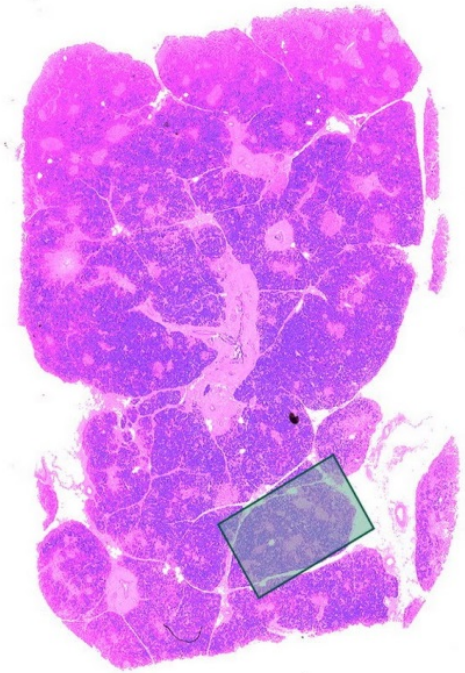
“scattered” islets (<8 nuclei)

Insulin + CK19 duct cells

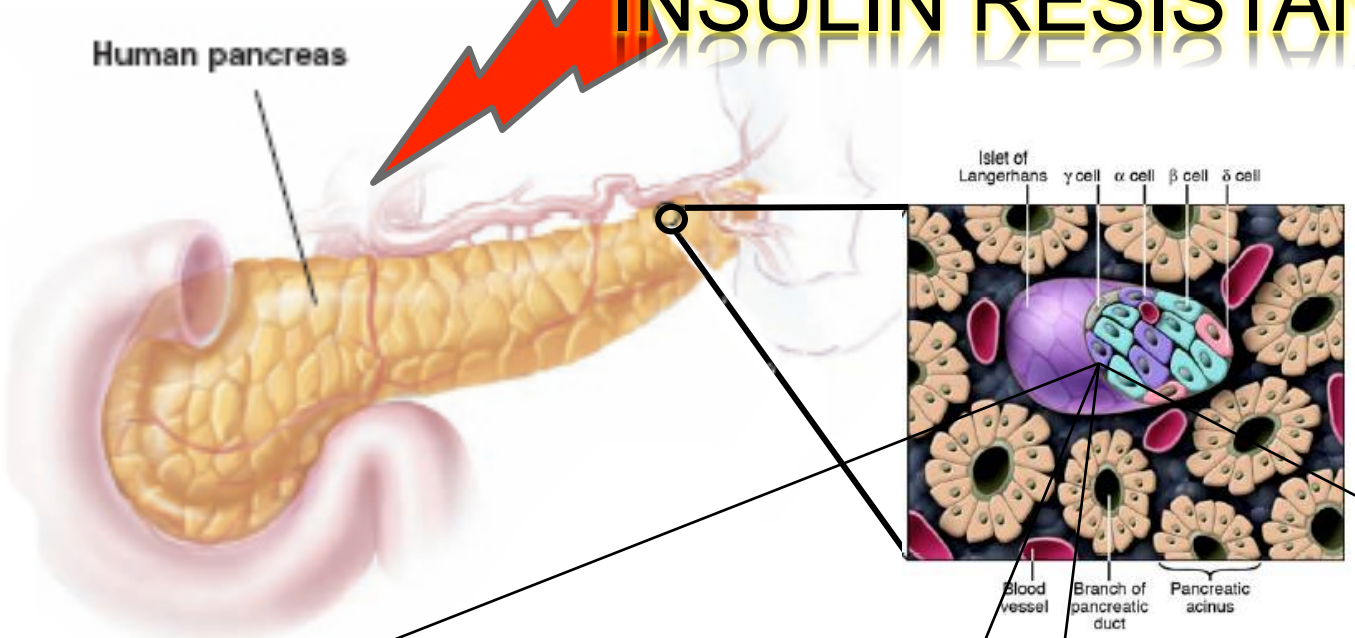
**Transdifferenziazione**

Insulin + glucagon double positive cells

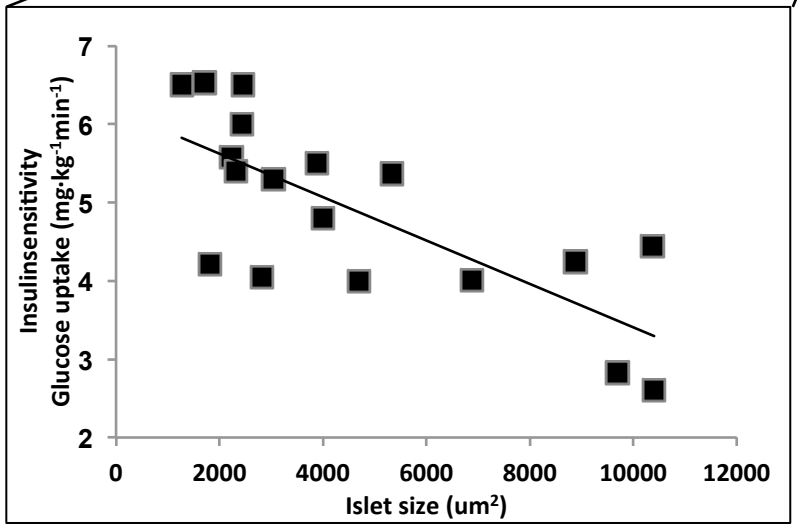


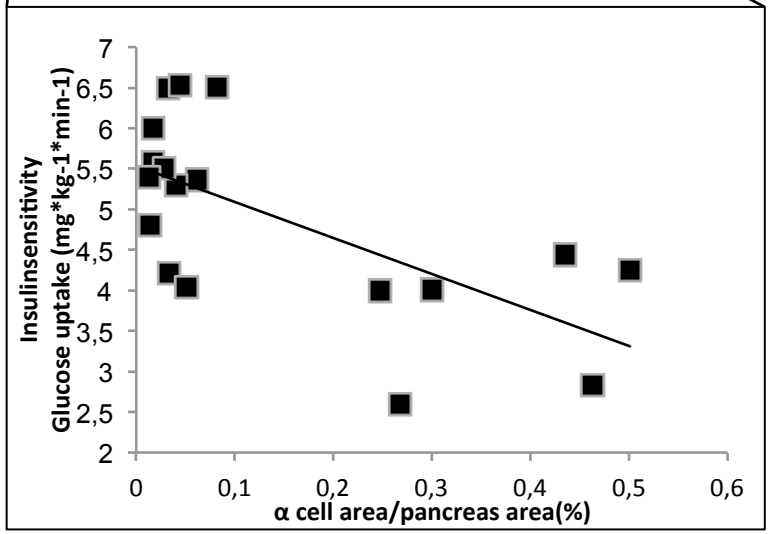


# INSULIN RESISTANCE



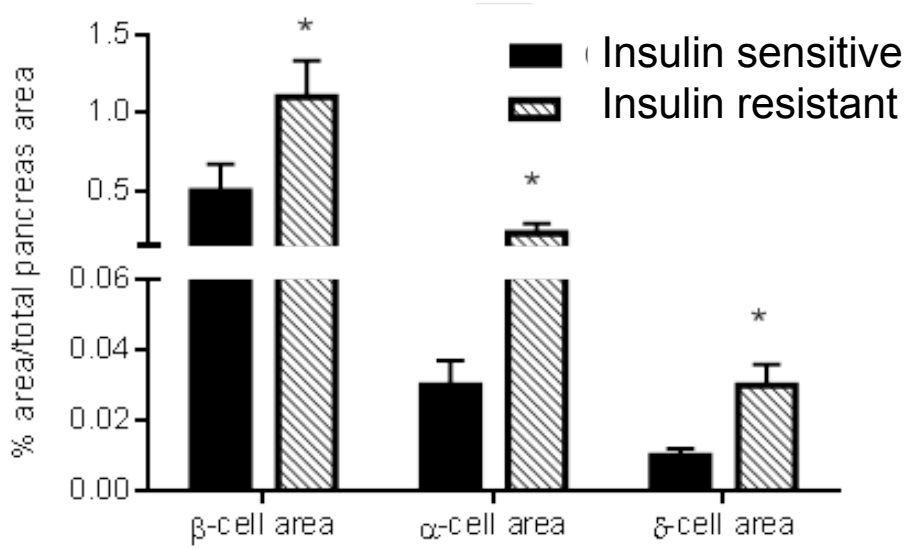

- ↑ Islet size
- ↑ Glucagon Area

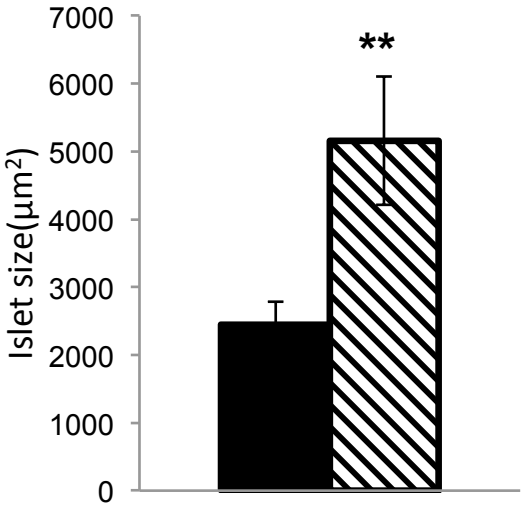


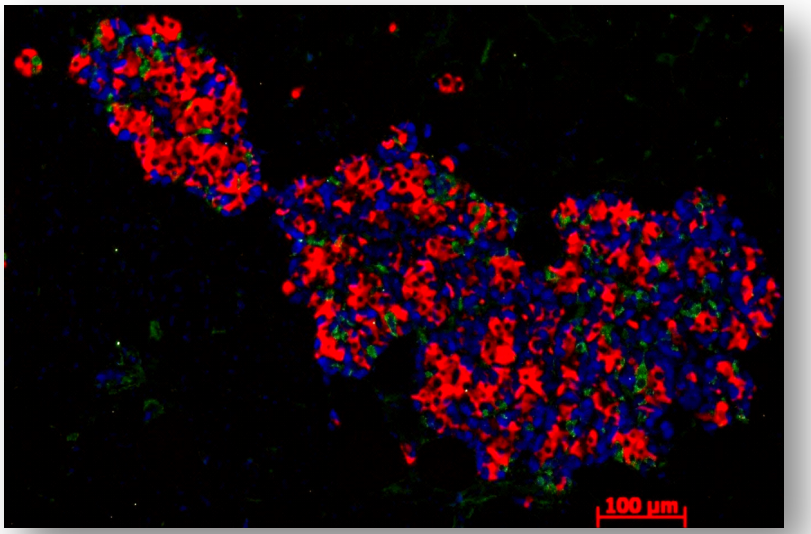



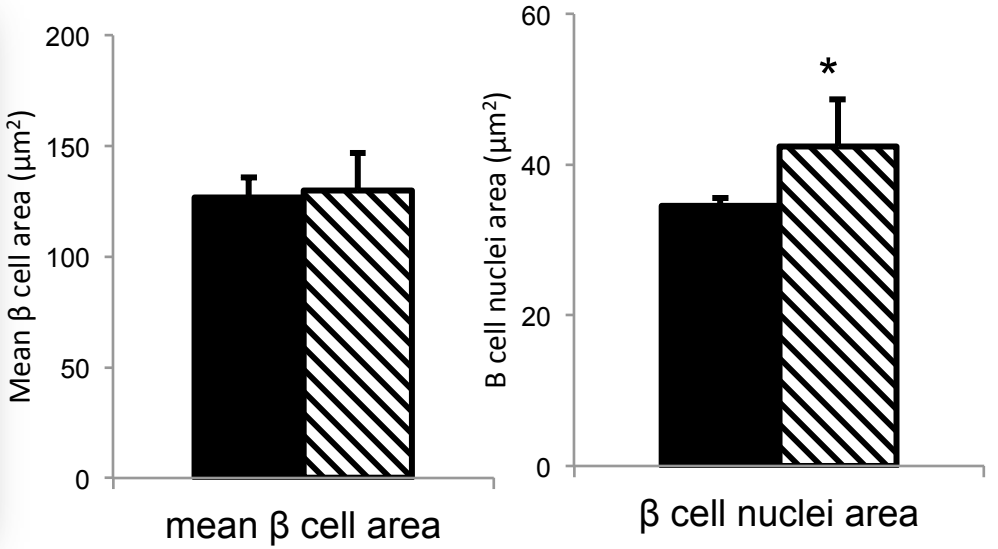

Mezza T et al. Diabetes 2014

# Morfologia insulare



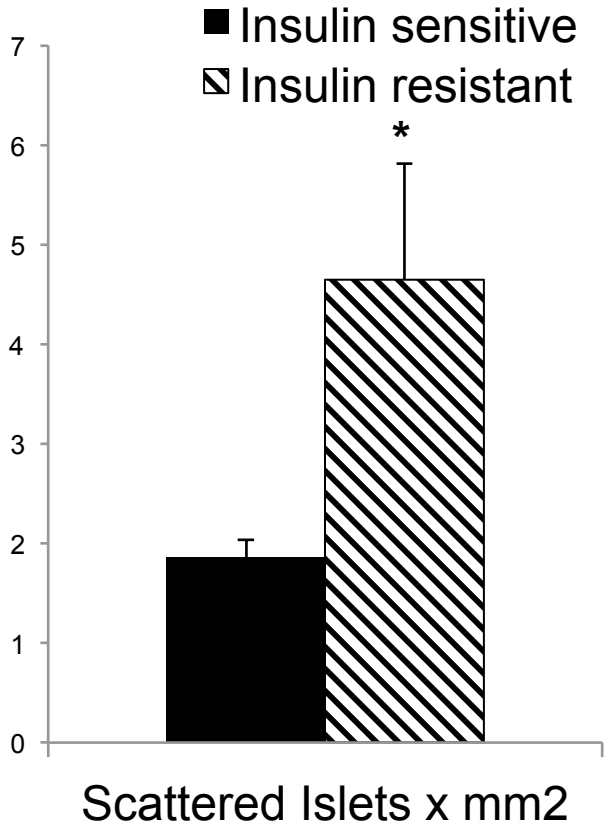

Mezza T et al. Diabetes 2014

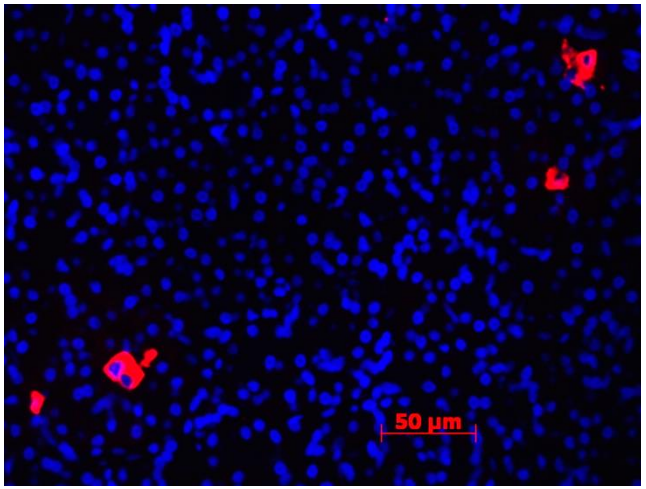
**Quali sono i meccanismi responsabili della alterata morfologia insulare in condizioni di insulinoresistenza?**

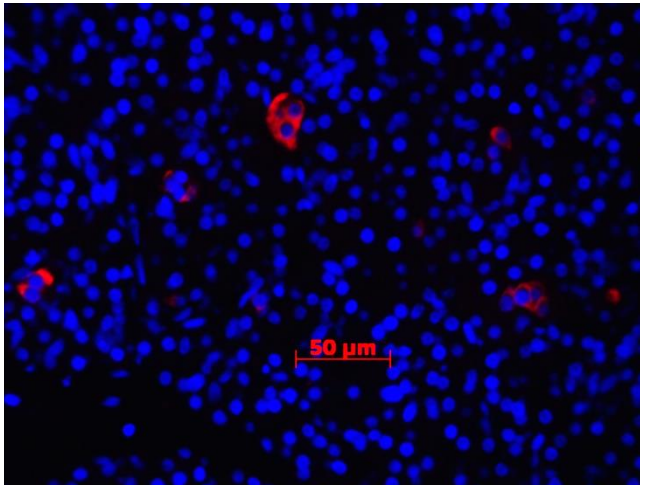
**No Proliferazione (Ki67)**

**No Apoptosi (Tunel)**

# Neogenesi: scattered islets



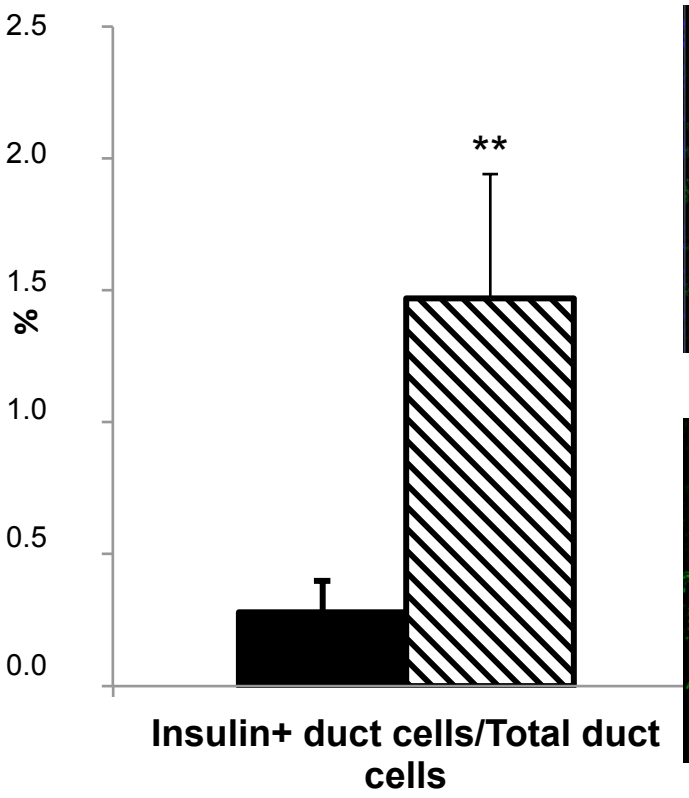



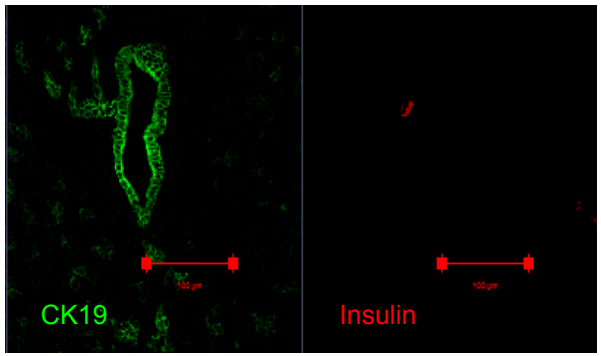



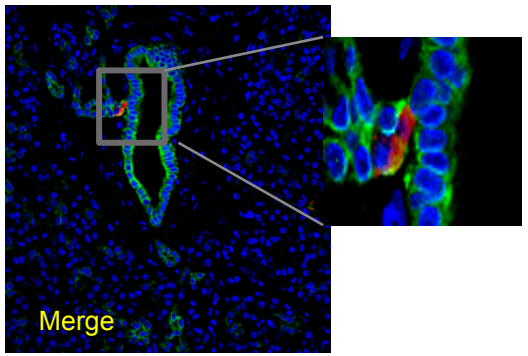

**n.: 9 IS vs 9 IR,**
*** p<0.05, **p<0.01**

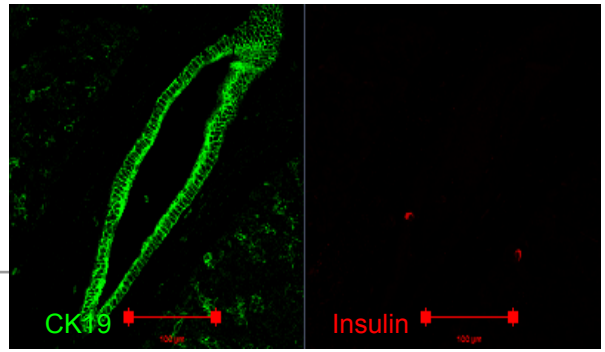
Mezza T et al. Diabetes 2014

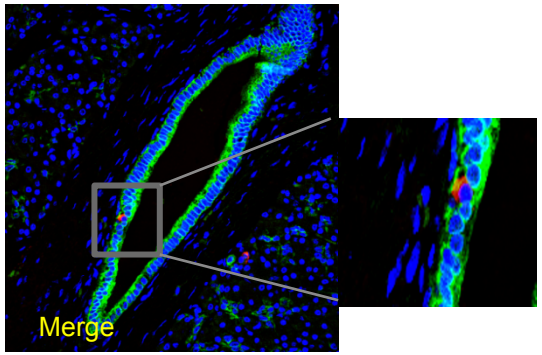
# Neogenesi: Cellule duttali



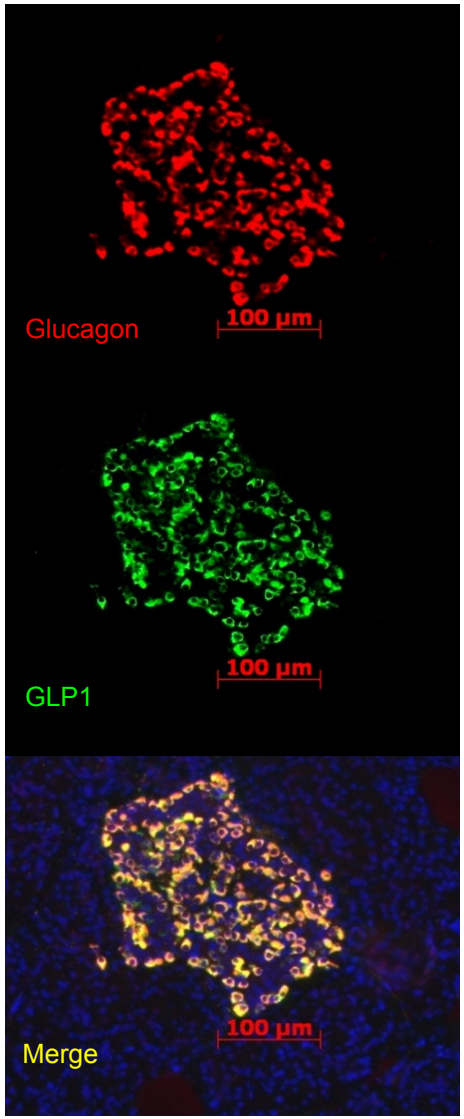



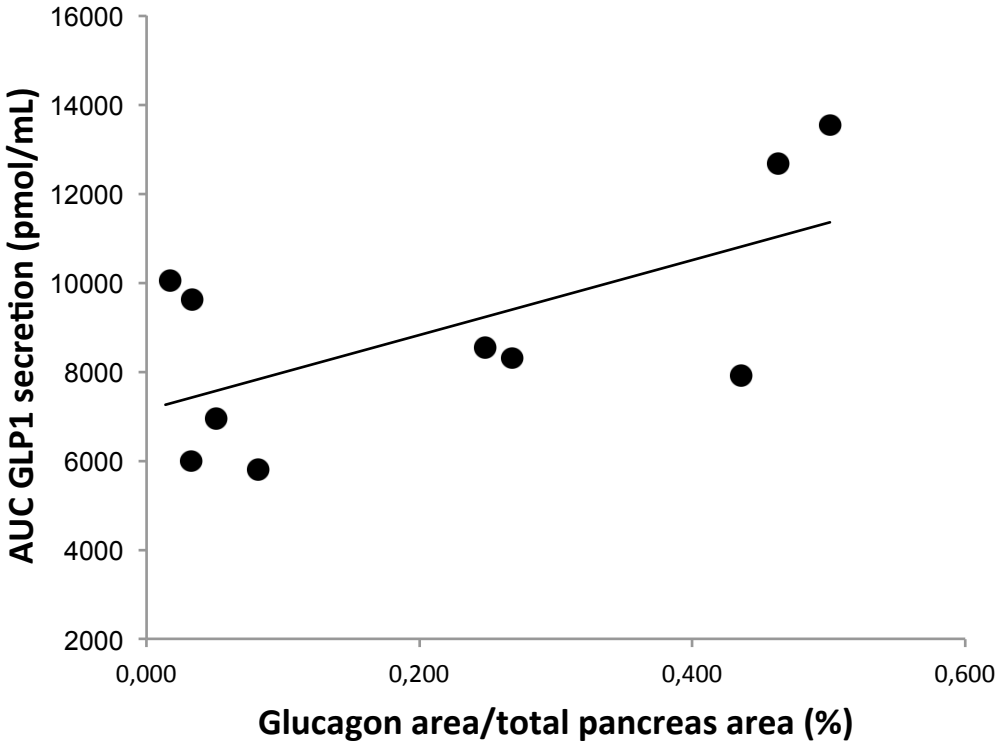




**n.: 9 control vs 9 IR,**
*** p<0.05, **p<0.01**

Mezza T et al. Diabetes 2014

# GLP-1 intrainsulare correla con secrezione

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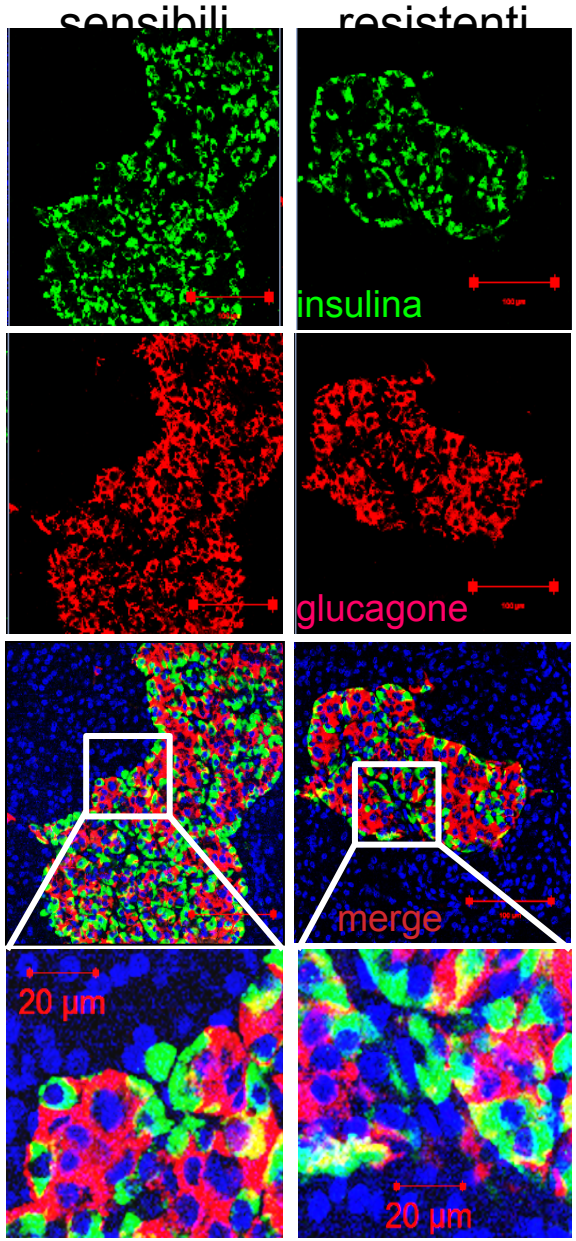
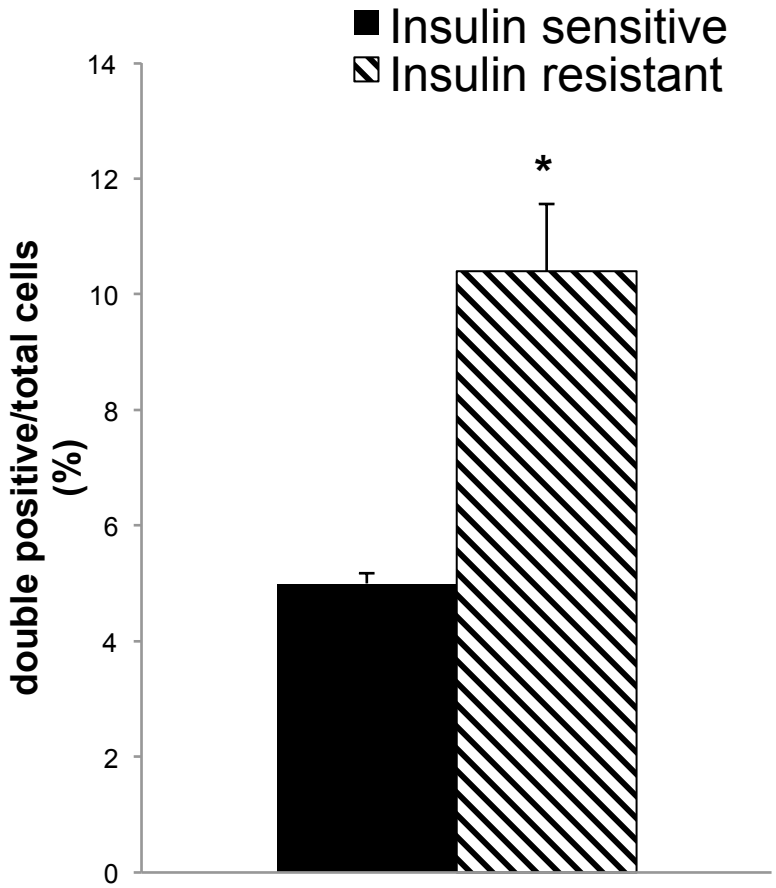
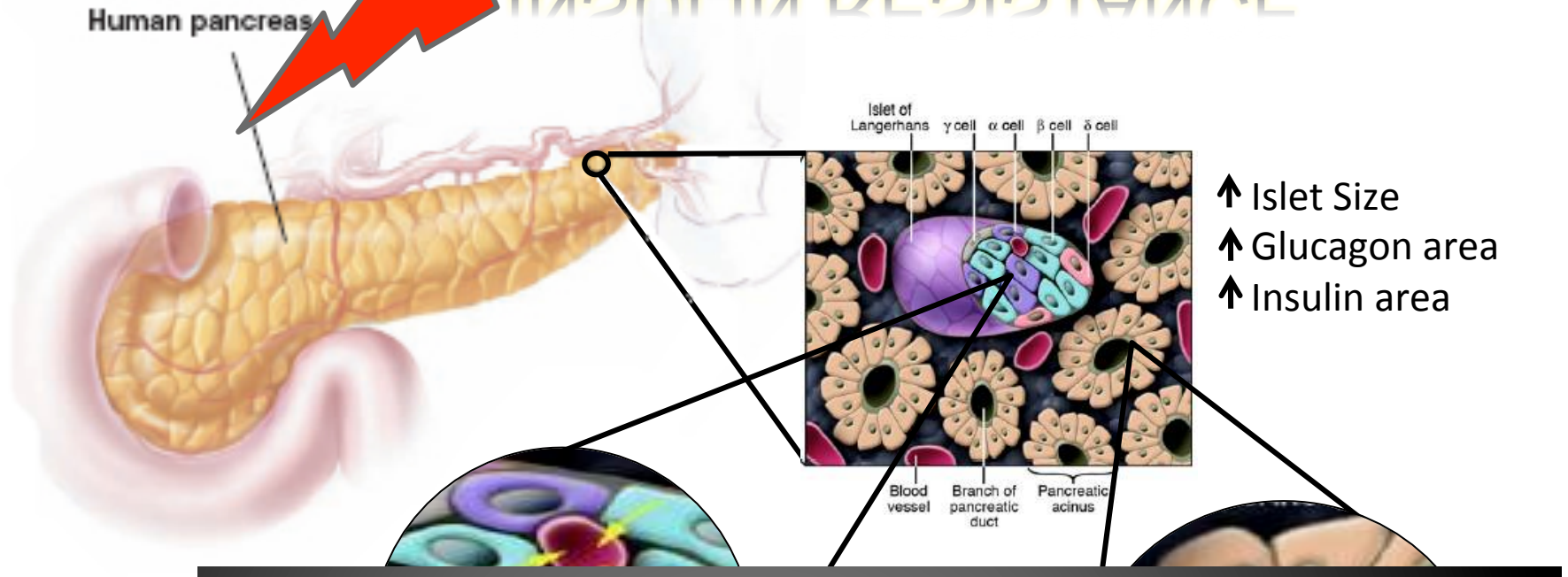
# Transdifferenziazione α →β




**Mezza T.** Diabetes 63;994; 2014

# INSULIN RESISTANCE




- ↑ Islet Size
- ↑ Glucagon area
- ↑ Insulin area

**NEOGENESI**
**TRANSDIFFERENTIAZIONE $\alpha$-Cells**
**EFFETTI GLP-1 mediati**

↑α-cells

ting

ts

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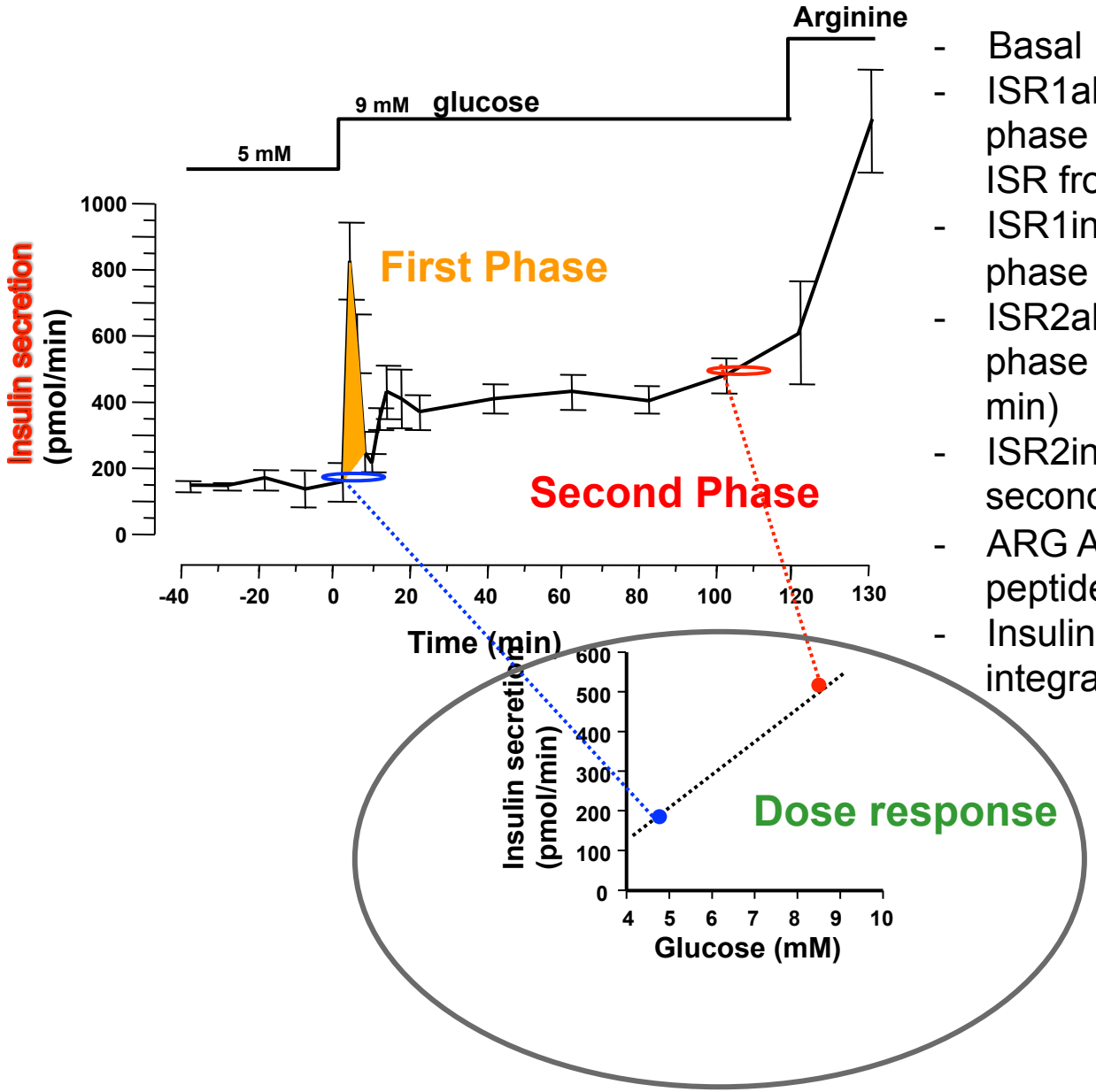
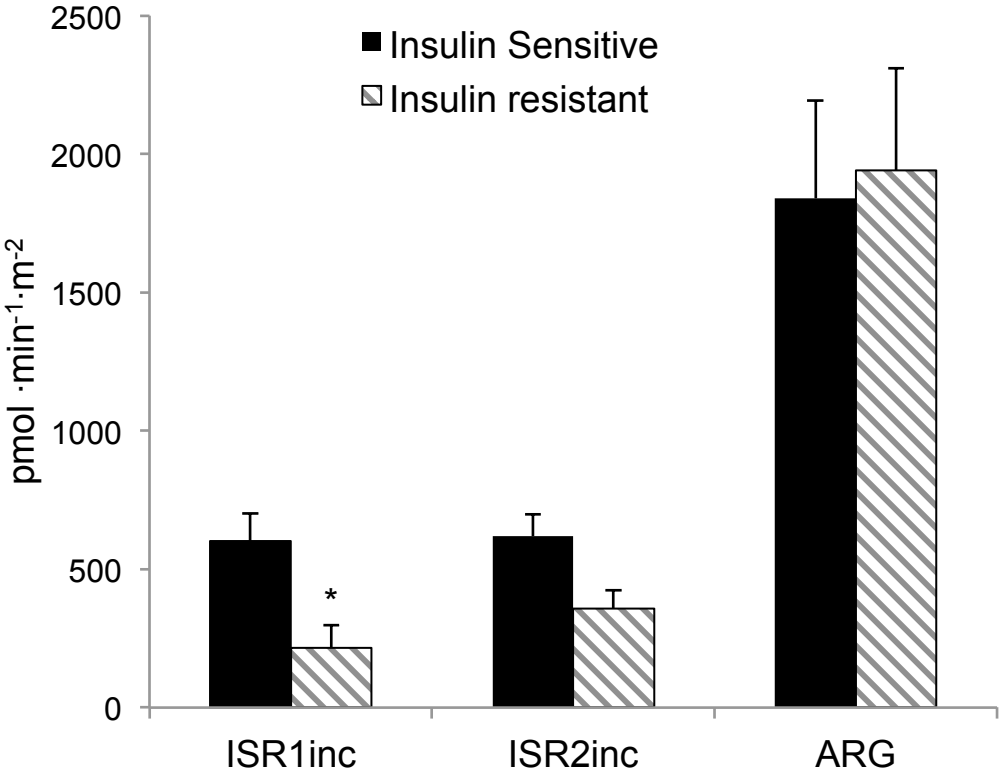
# Secrezione – Modellistica

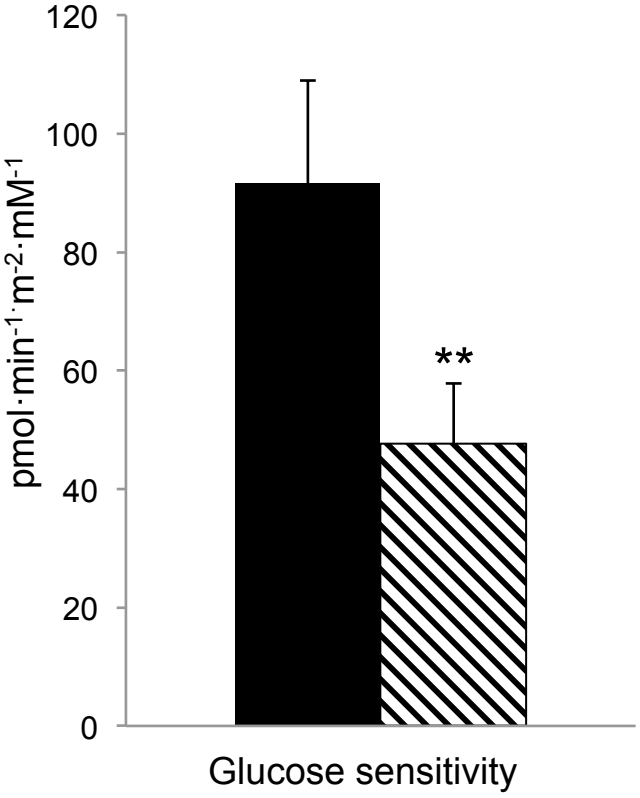



- Basal Insulin secretion
- ISR1abs Absolute response of first phase insulin secretion (mean integral ISR from 0 to 6 min)
- ISR1inc Incremental response of first phase (ISR1abs-ISRb)
- ISR2abs Absolute response of second phase (mean integral ISR from 100 a120 min)
- ISR2inc Incremental Response of second phase (ISR2abs-ISRb)
- ARG Arginine response (130 min C-peptide - 120 min C-peptide)
- Insulin clearance (ISR2abs/mean integrale da 100 a 120 min)

glucose sensitivity (ISR2inc/ (Glucose steadystate-basal glucose))

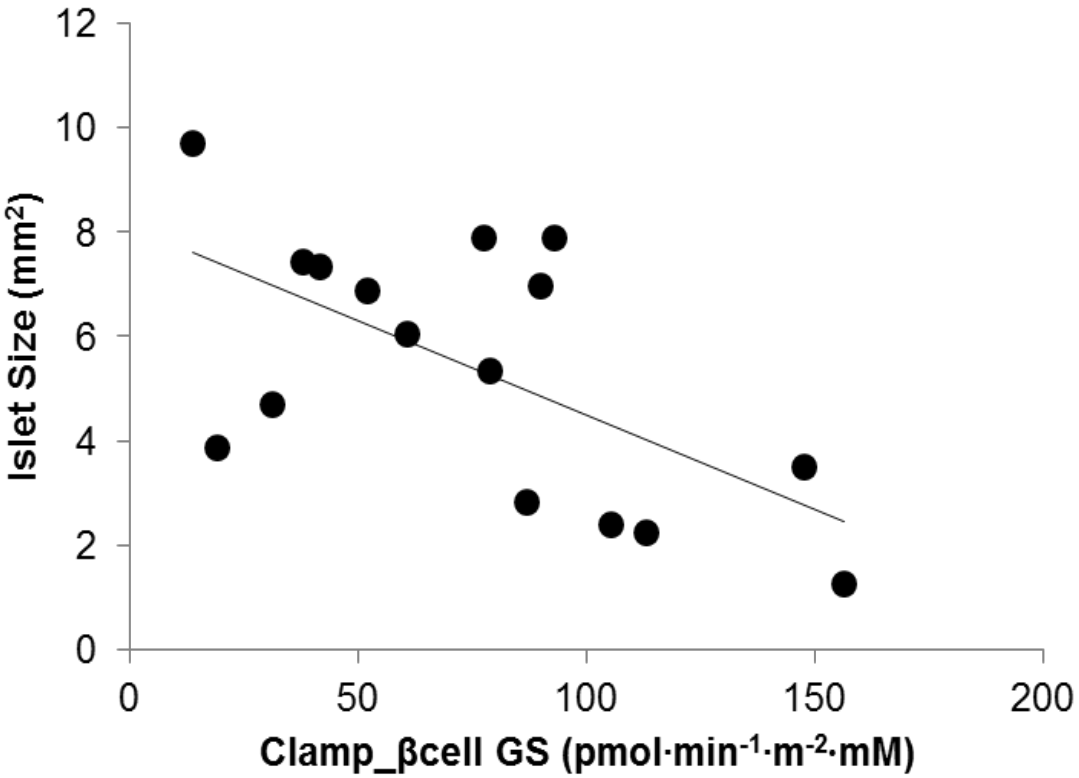
# Secrezione Insulinica e Glucose Sensitivity




Mezza T. et al. Submitted

# Aumento massa: un possibile stimolo

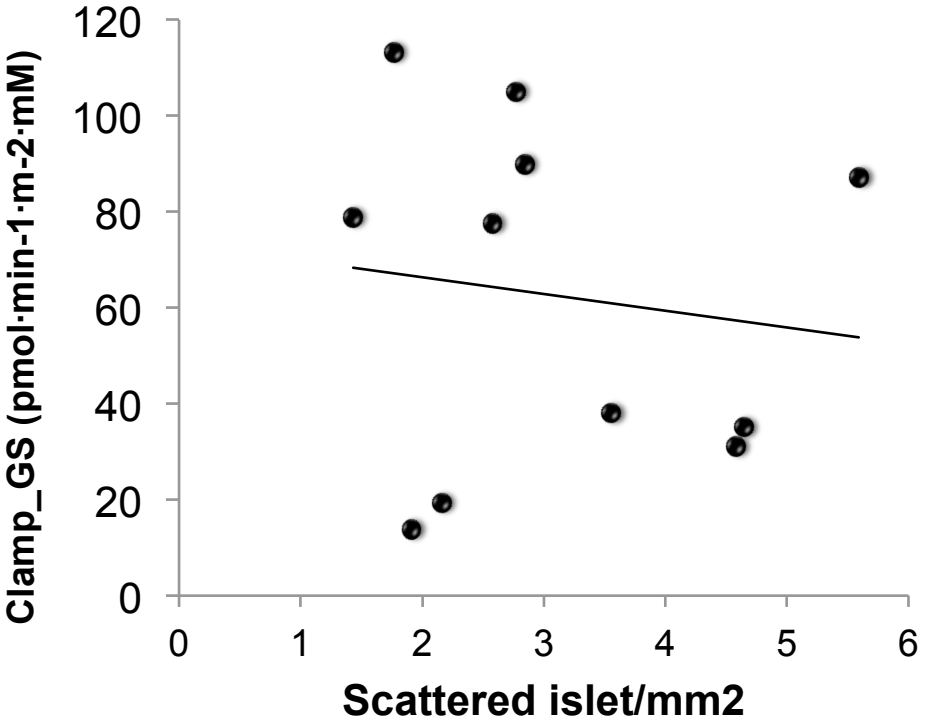


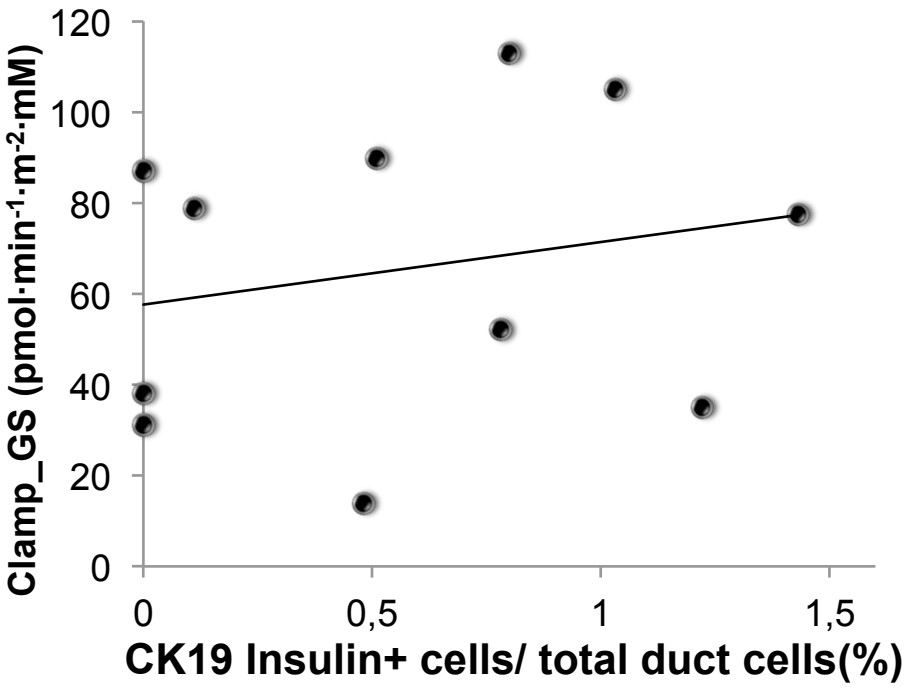

Mezza T. et al. Submitted

# Quale è il meccanismo “triggered” dalla alterata funzione beta cellulare?

- NEOGENESI
- TRANSDIFFERENTIAZIONE α -> $\beta$

# Neogenesi e Glucose Sensitivity

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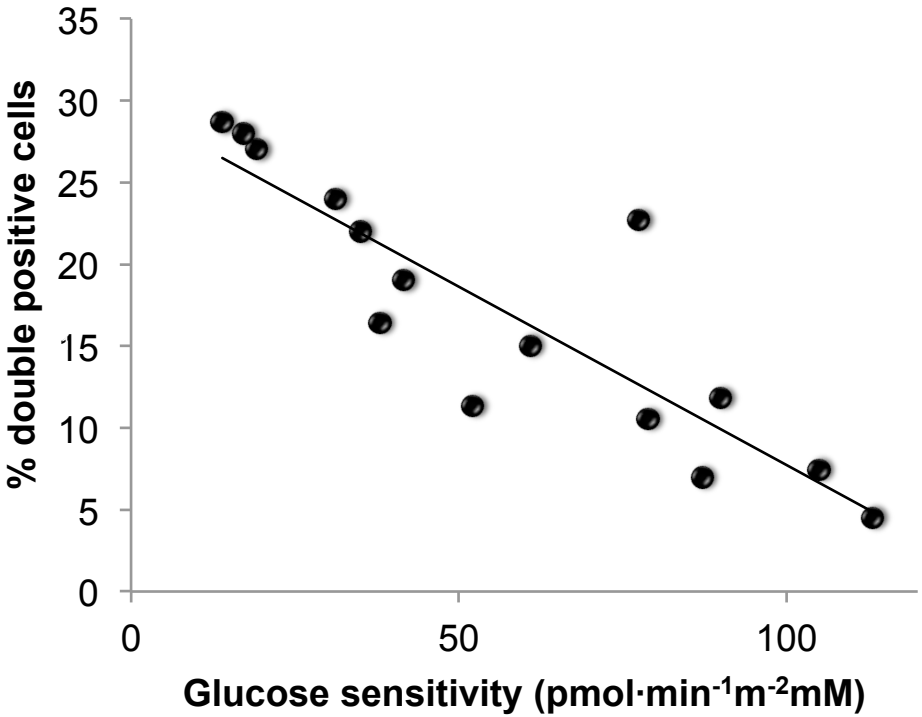
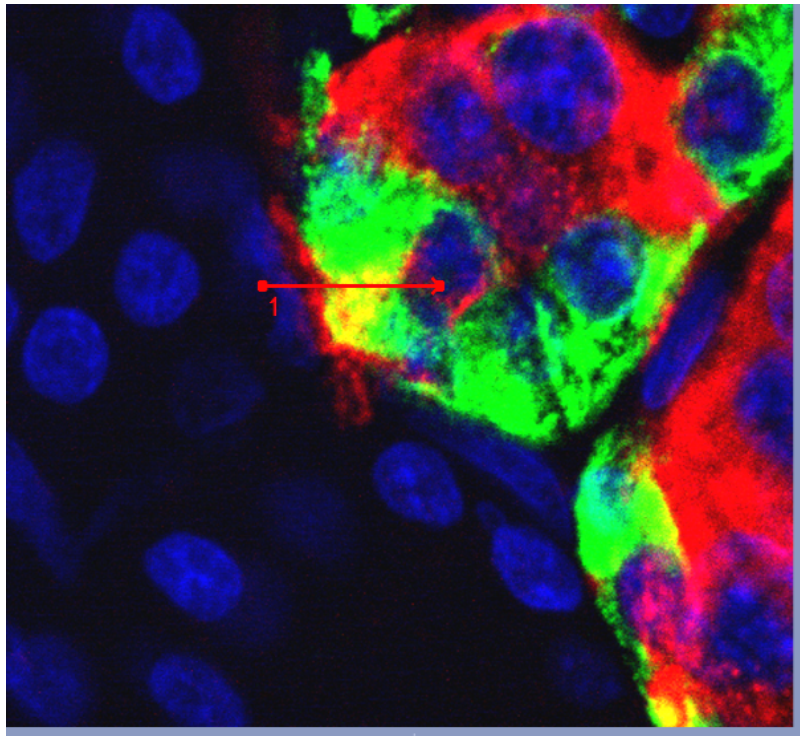
# Transdifferenziazione e Glucose Sensitivity




Mezza T. et al. Submitted

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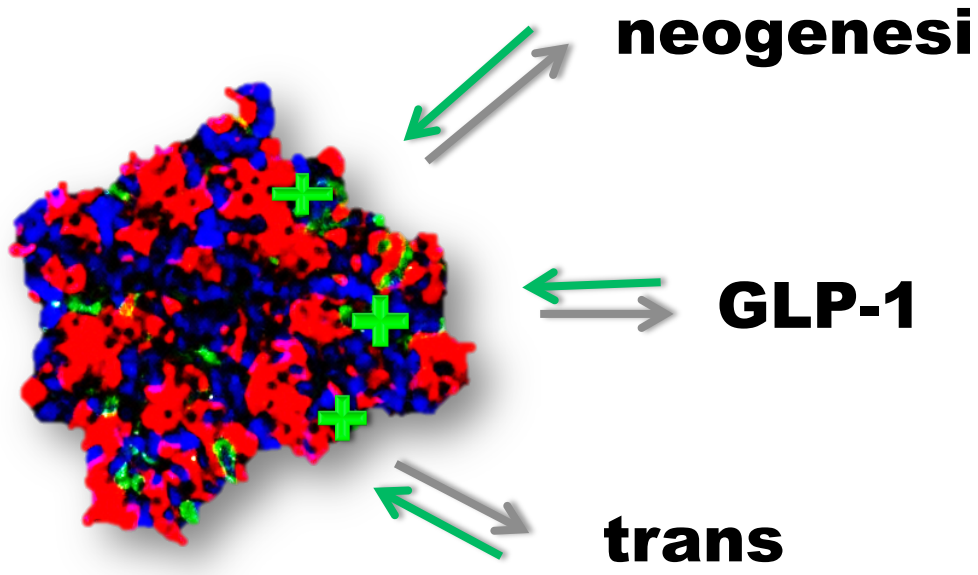
# PROSPETTIVE




- ✓ Individuare meccanismi molecolari alla base della plasticità insulare
- ✓ Nuovi target terapeutici per preservare la massa beta cellulare in pazienti non diabetici (a rischio)

# RINGRAZIAMENTI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**Andrea Giaccari**

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