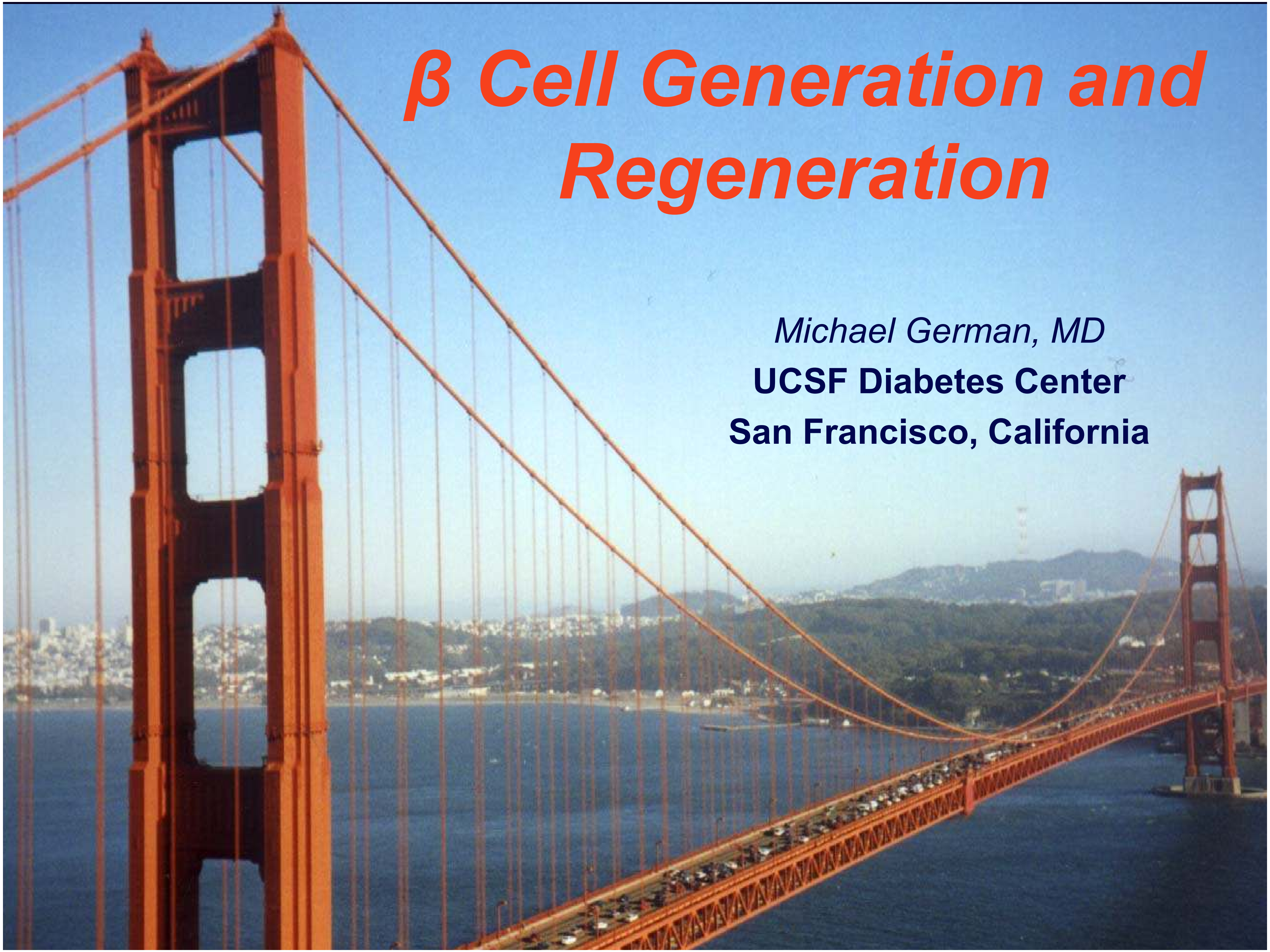
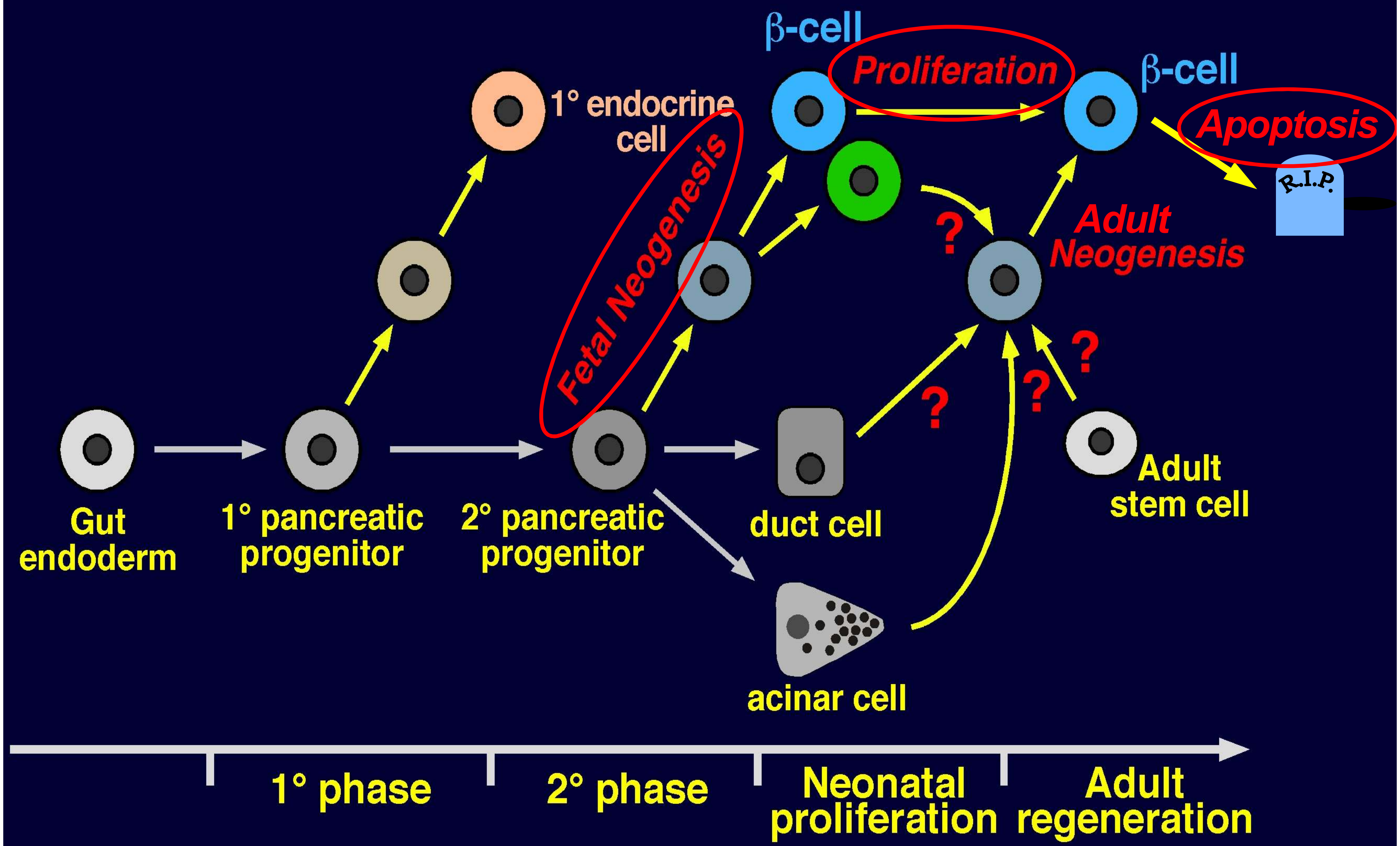
β Cell Generation and Regeneration

Michael German, MD
UCSF Diabetes Center
San Francisco, California



Where do β cells come from?



Rfx6

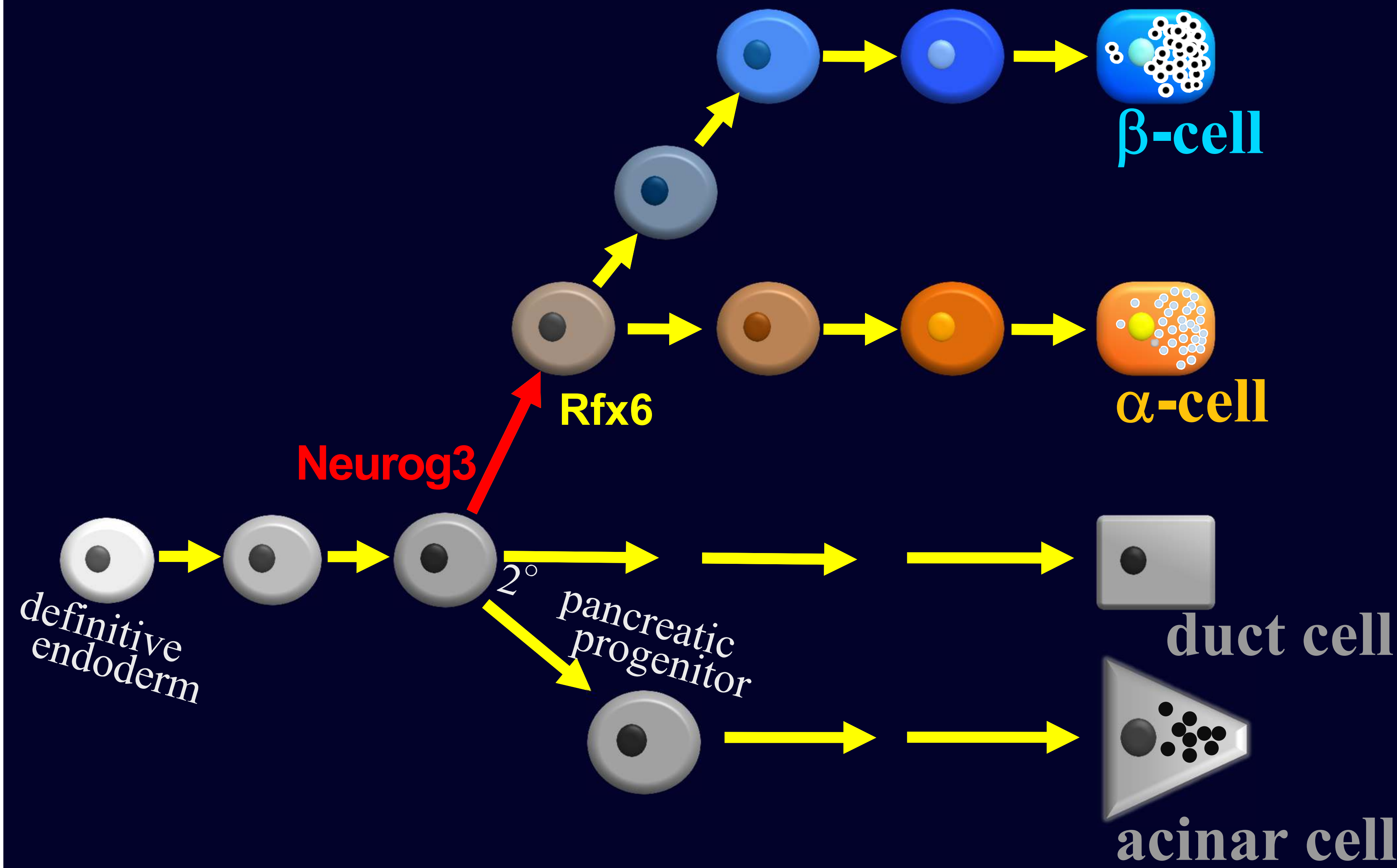
Takeshi Miyatsuka, MD, PhD

Stuart Smith, PhD

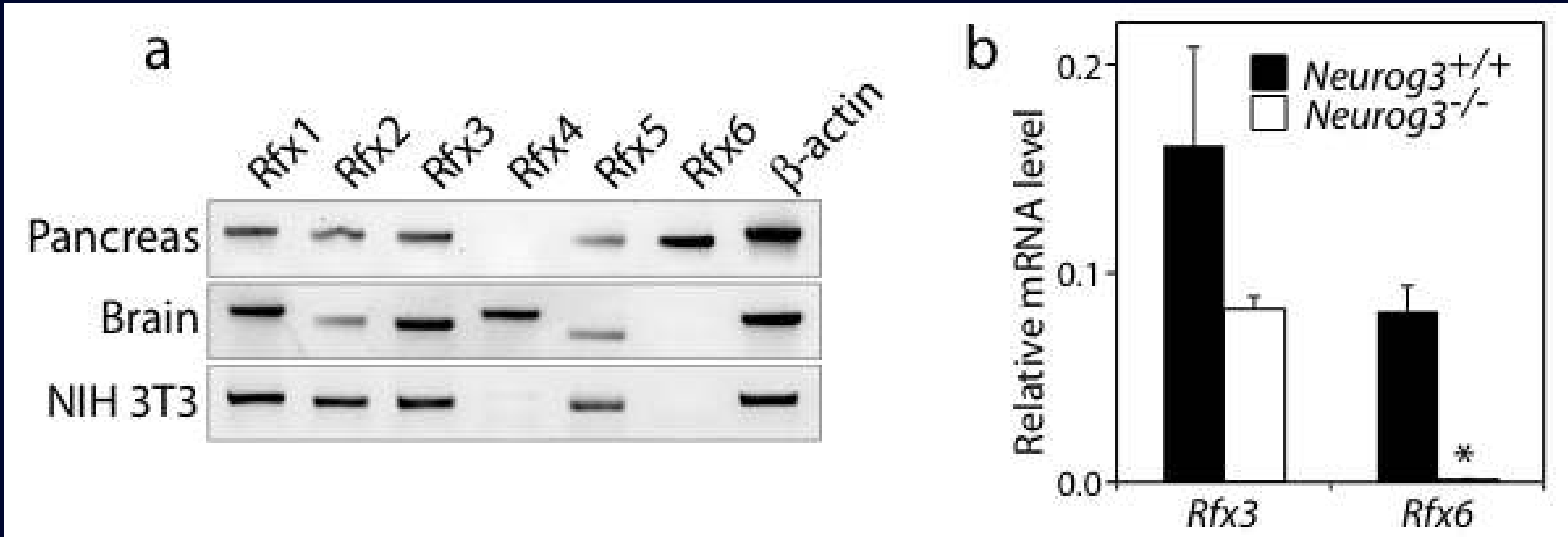
Nina Kishimoto

David Scheel

Islet Cell Lineages

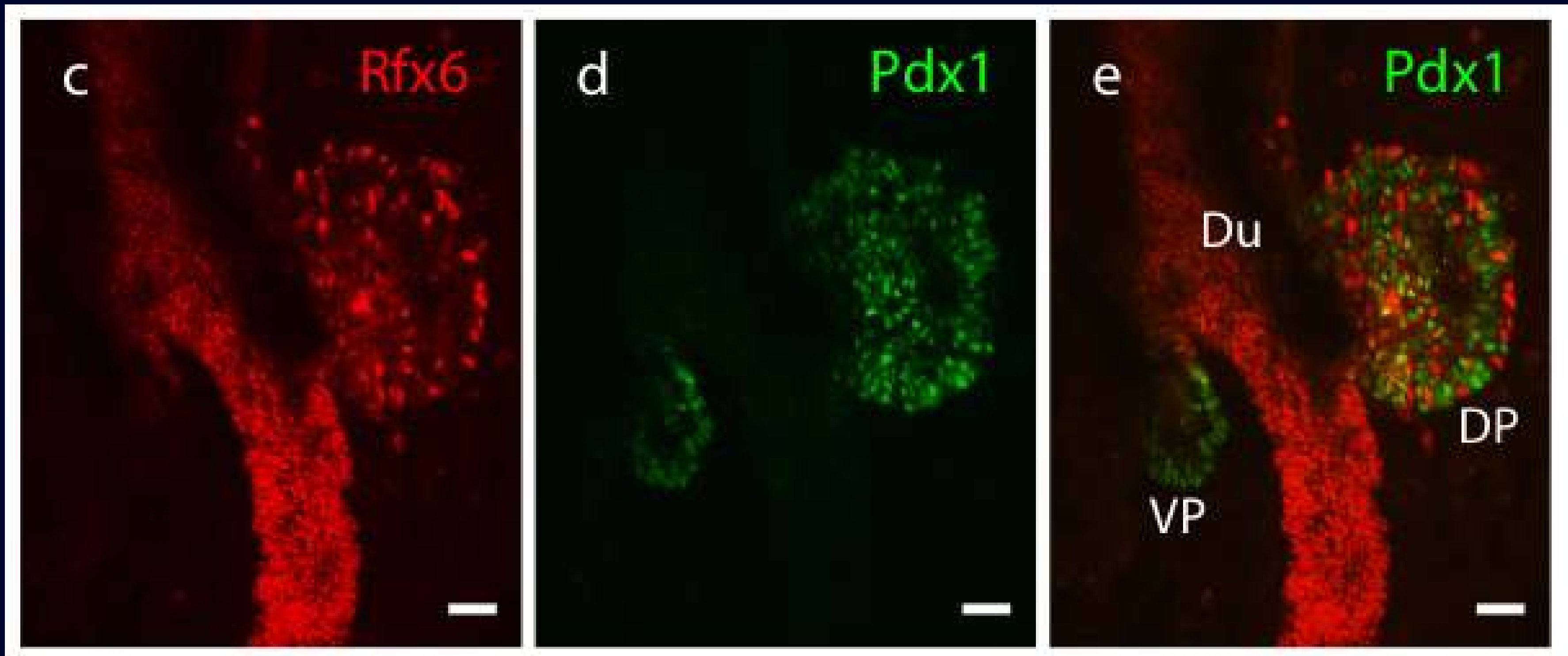


Expression Profile of RFX Factors



Stuart Smith

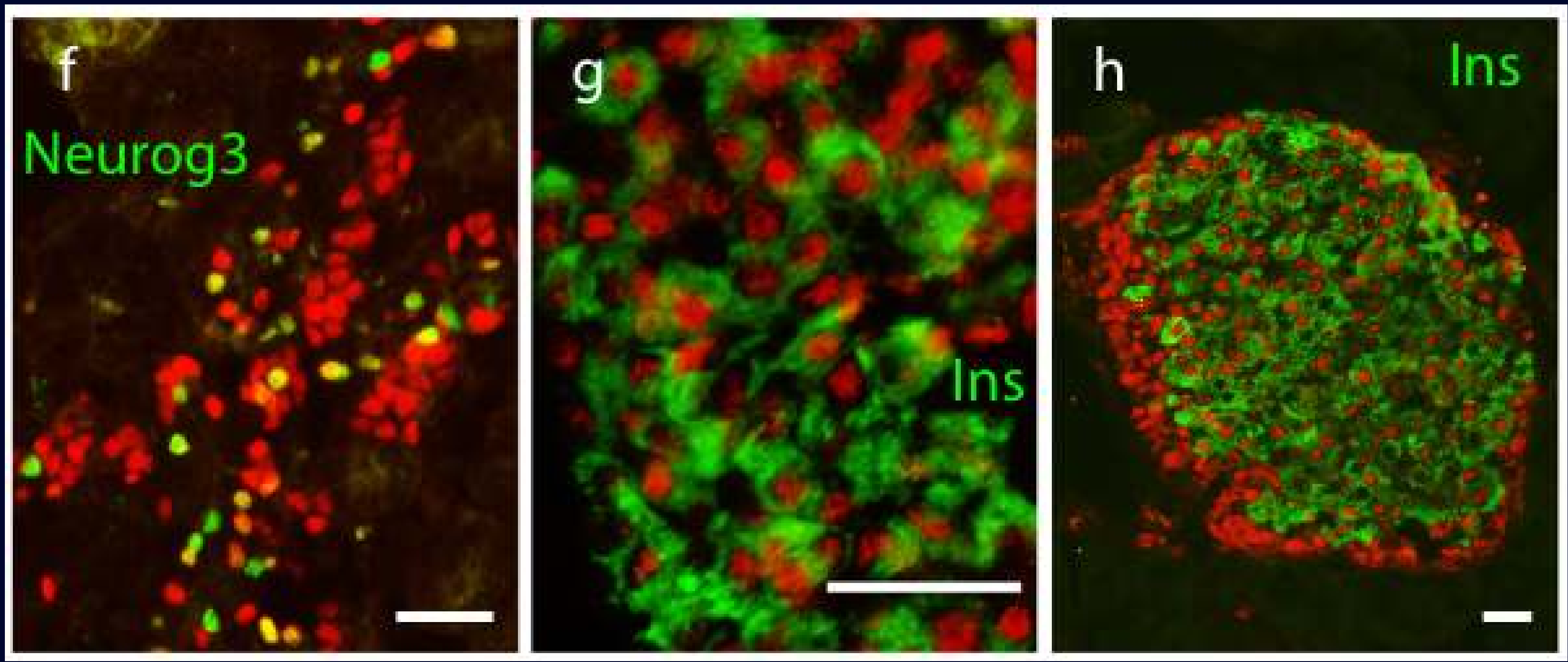
Rfx6 Expression at E10



Nina Kishimoto

Rfx6 Expression

Rfx6



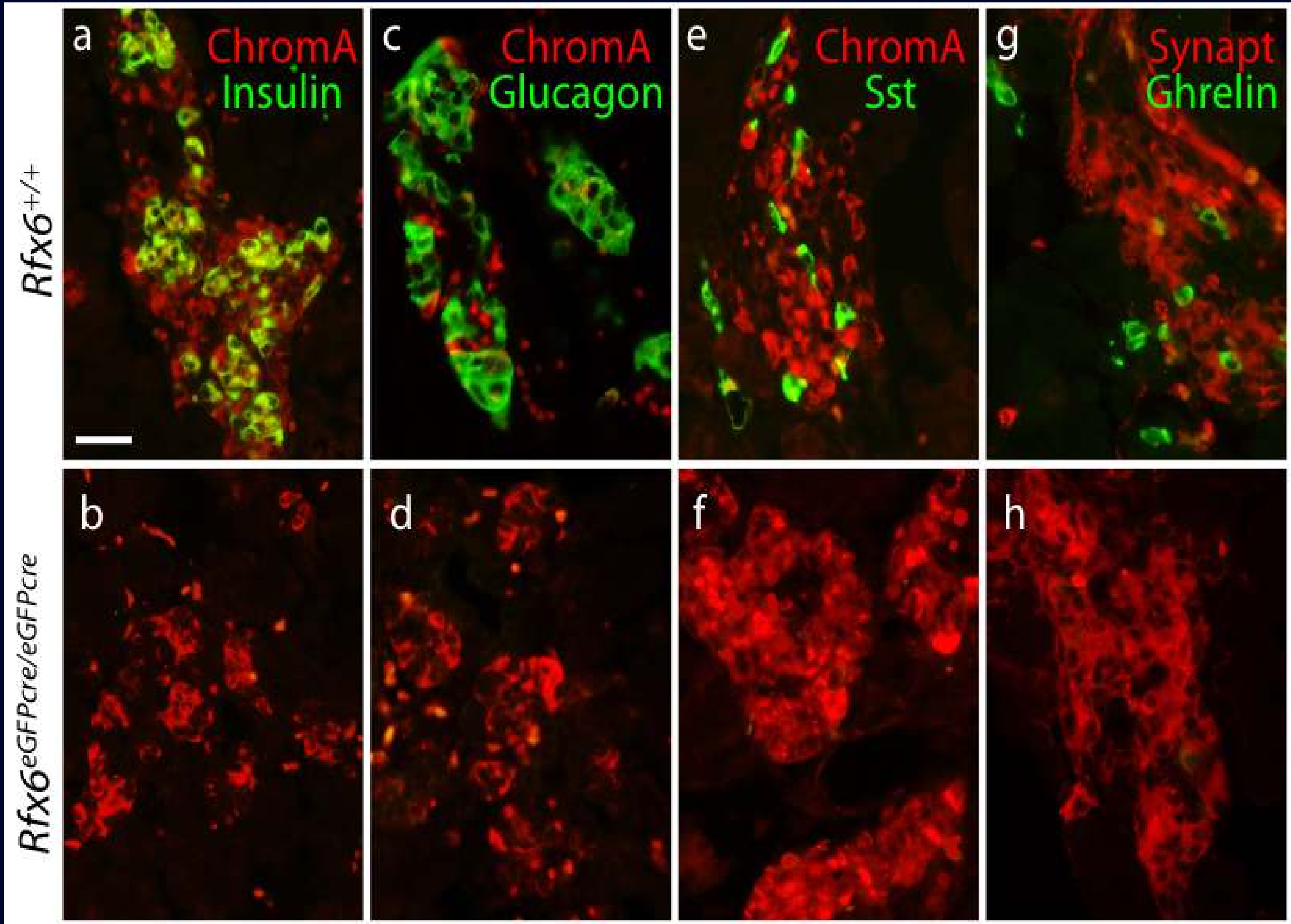
E14.5 E18.5 Adult

Nina Kishimoto

Rfx6$^{-/-}$ Mice at P1

Stuart Smith & David Scheel

Rfx6$^{-/-}$ Mice at E17.5



Stuart Smith & David Scheel

Mitchell-Riley Syndrome

Neonatal diabetes, with hypoplastic pancreas, intestinal atresia and gall bladder hypoplasia: search for the aetiology of a new autosomal recessive syndrome

J. Mitchell[1] · Z. Punthakee[1] · B. Lo[2] · C. Bernard[3] · K. Chong[2] · C. Newman[4] · L. Cartier[5] · V. Desilets[5] · E. Cutz[6] · I. L. Hansen[7] · P. Riley[8] · C. Polychronakos[1,9]

Diabetolgia, 2004.

Clinical Report

A Further Example of a Distinctive Autosomal Recessive Syndrome Comprising Neonatal Diabetes Mellitus, Intestinal Atresias and Gall Bladder Agenesis

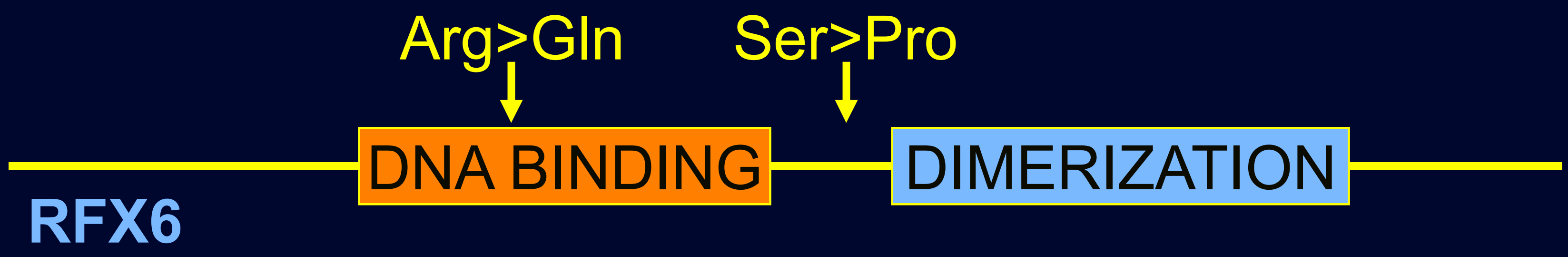
Louise Chappell,[1] Shaun Gorman,[2] Fiona Campbell,[3] Sian Ellard,[4] Gillian Rice,[5] Angus Dobbie,[6*] and Yanick Crow[2,5]

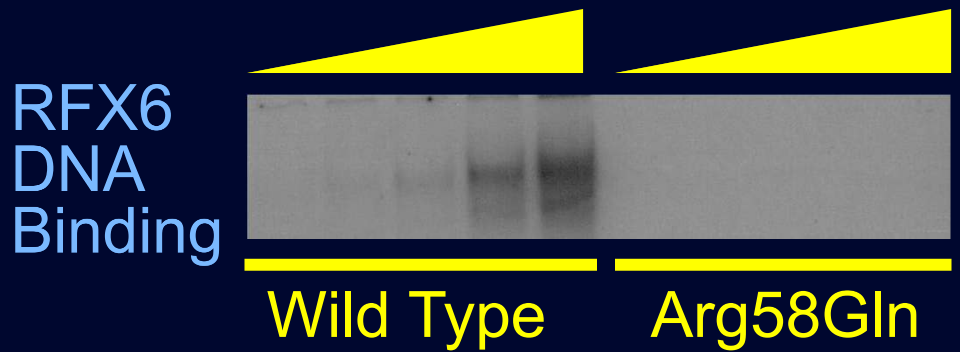
Am. J. Med. Genetics, 2008.

Mutations in Human Patients.

5 Probands tested:

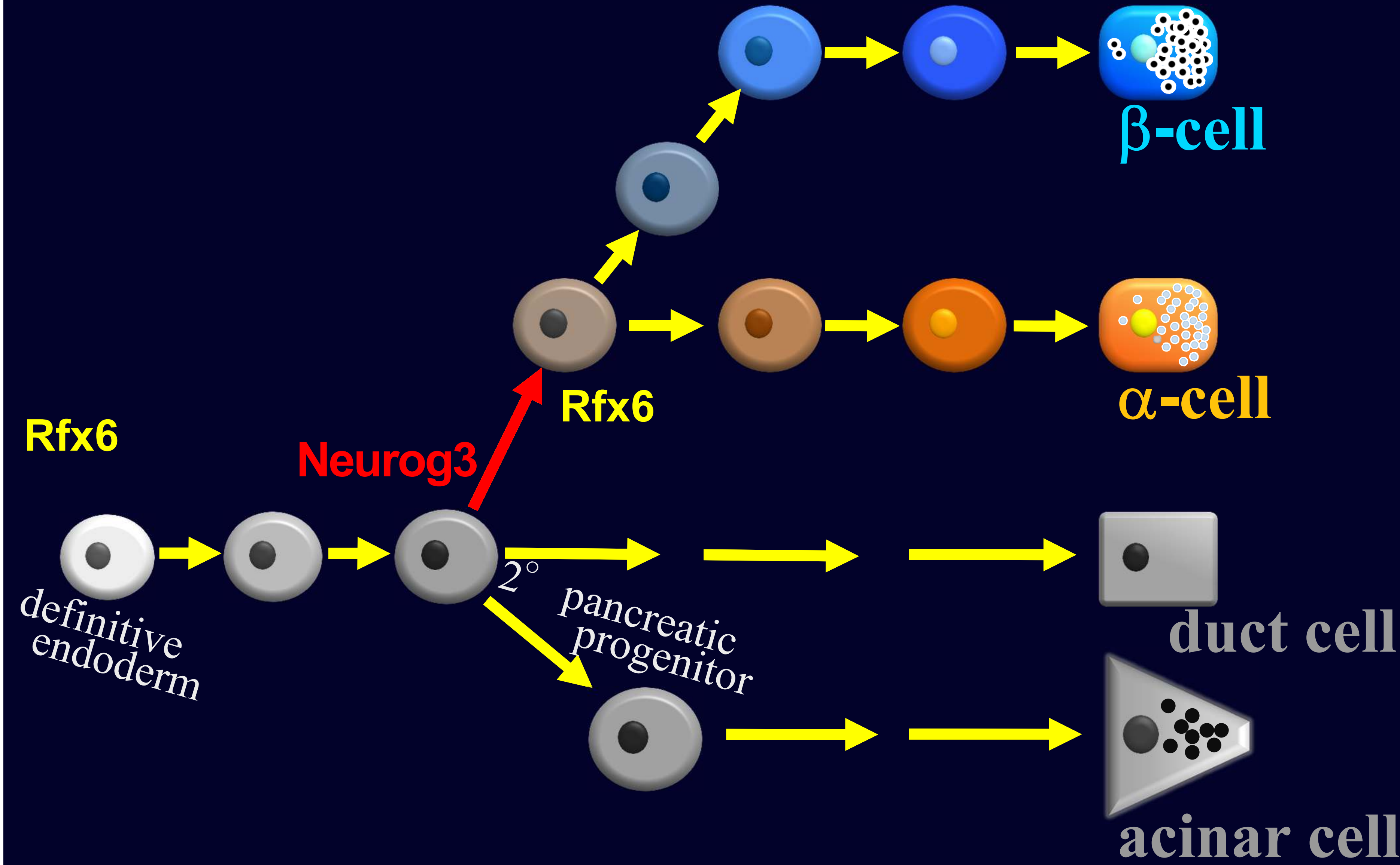
4 Homozygous *RFX6* mutations.
1 Compound heterozygote.
Splicing site and missense mutations.

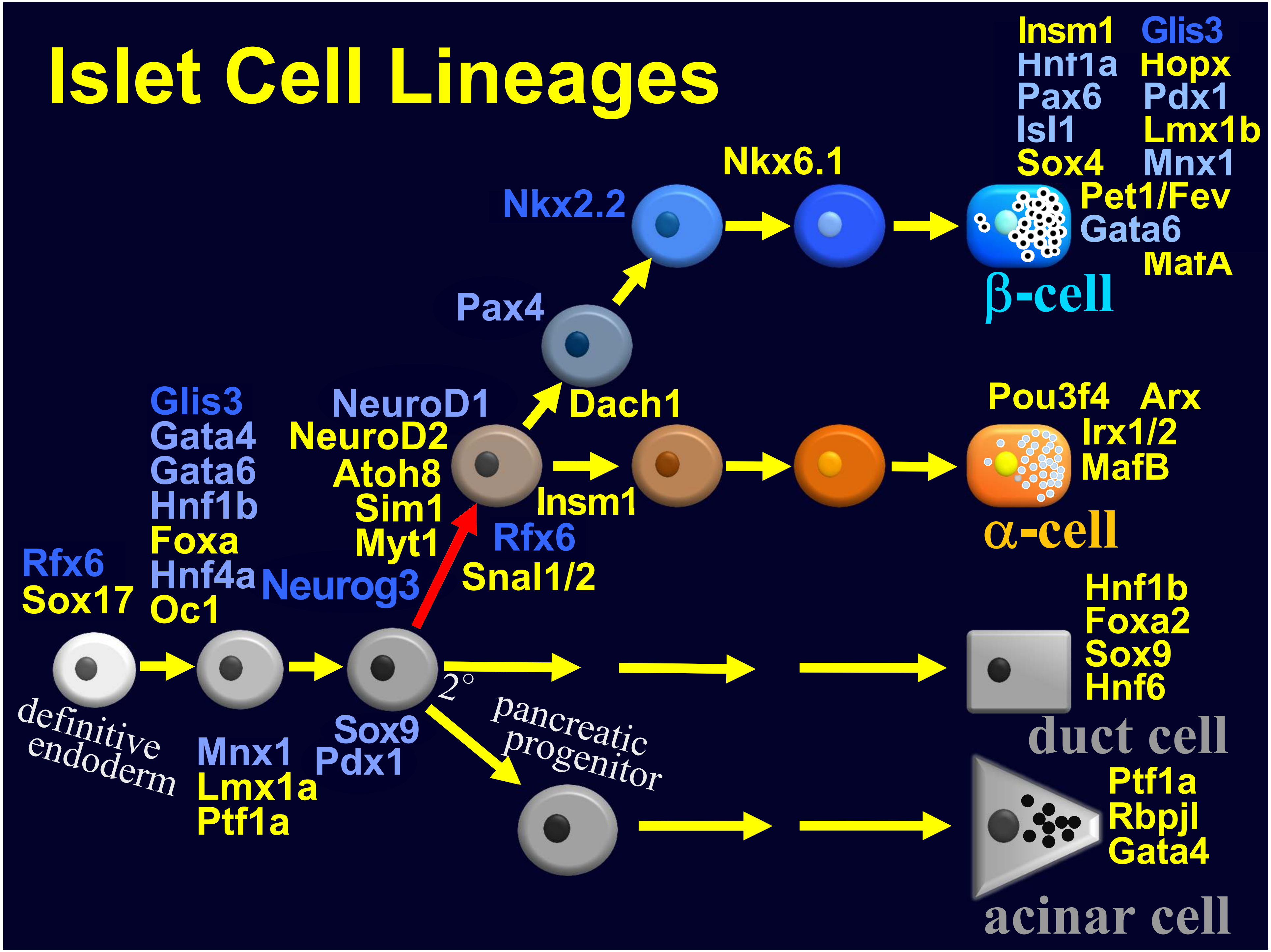




Constantin Polychronakos
Stuart Smith

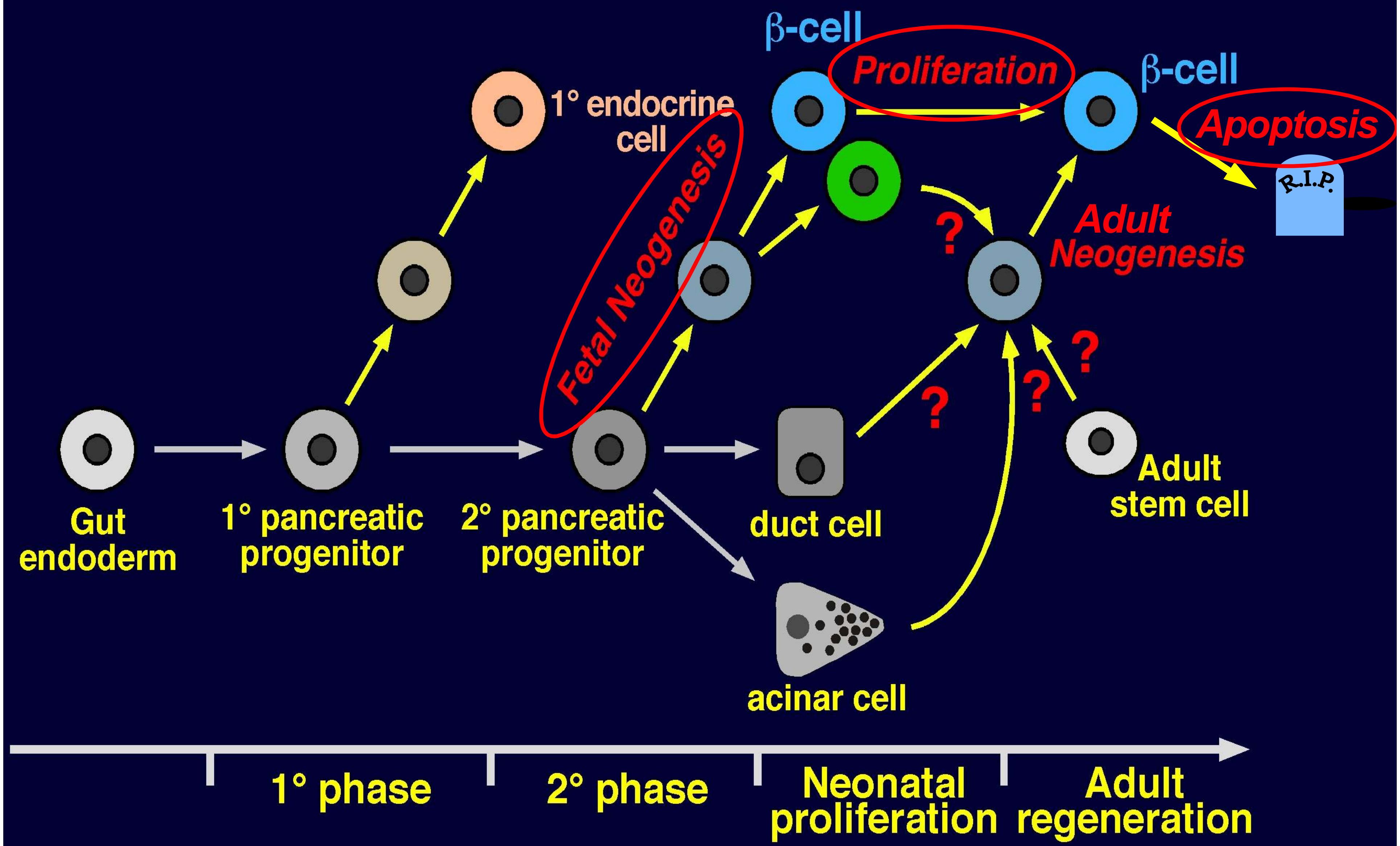
Islet Cell Lineages





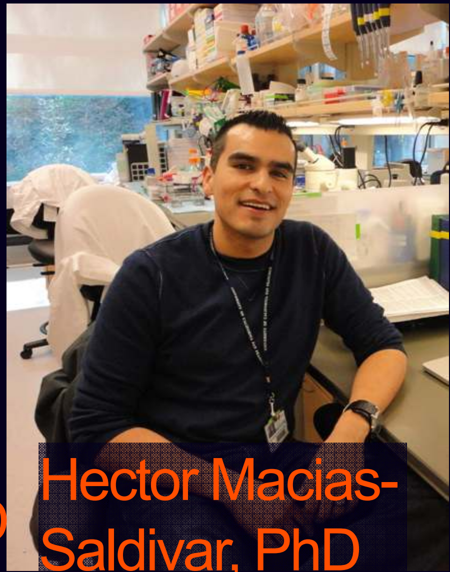
Islet Cell Lineages
Insm1
Hnf1a
Pax6
Isl1
Sox4
Glis3
Hopx
Pdx1
Lmx1b
Mnx1
Pet1/Fev
Gata6
MafA
Nkx6.1
Nkx2.2
β-cell
Pax4
Glis3
Gata4
Gata6
Hnf1b
Foxa
Hnf4a
Oc1
NeuroD1
NeuroD2
Atoh8
Sim1
Myt1
Dach1
Insm1
Rfx6
Snal1/2
Pou3f4
Arx
Irx1/2
MafB
α-cell
Rfx6
Sox17
Neurog3
definitive endoderm
Mnx1
Lmx1a
Ptf1a
Sox9
Pdx1
2°
pancreatic progenitor
Hnf1b
Foxa2
Sox9
Hnf6
duct cell
Ptf1a
Rbpjl
Gata4
acinar cell

Where do β cells come from?



Physiologic Regulators of β Cell Turnover


Miles Berger, MD, PhD


Hector Macias-Saldivar, PhD


Hail Kim, MD, PhD


Takeshi Miyatsuka, MD, PhD


Chester Chamberlain, PhD


Greg Ku, MD, PhD


Nada Nekrep, PhD

Collaborators

UCSF:
- Miles Berger
- **Larry Tecott**
- Jean Regard
- **Sean Coughlin**
- **Bruce Conklin**
- **Gail Martin**
- Olov Andersson
- **Didier Stainier**

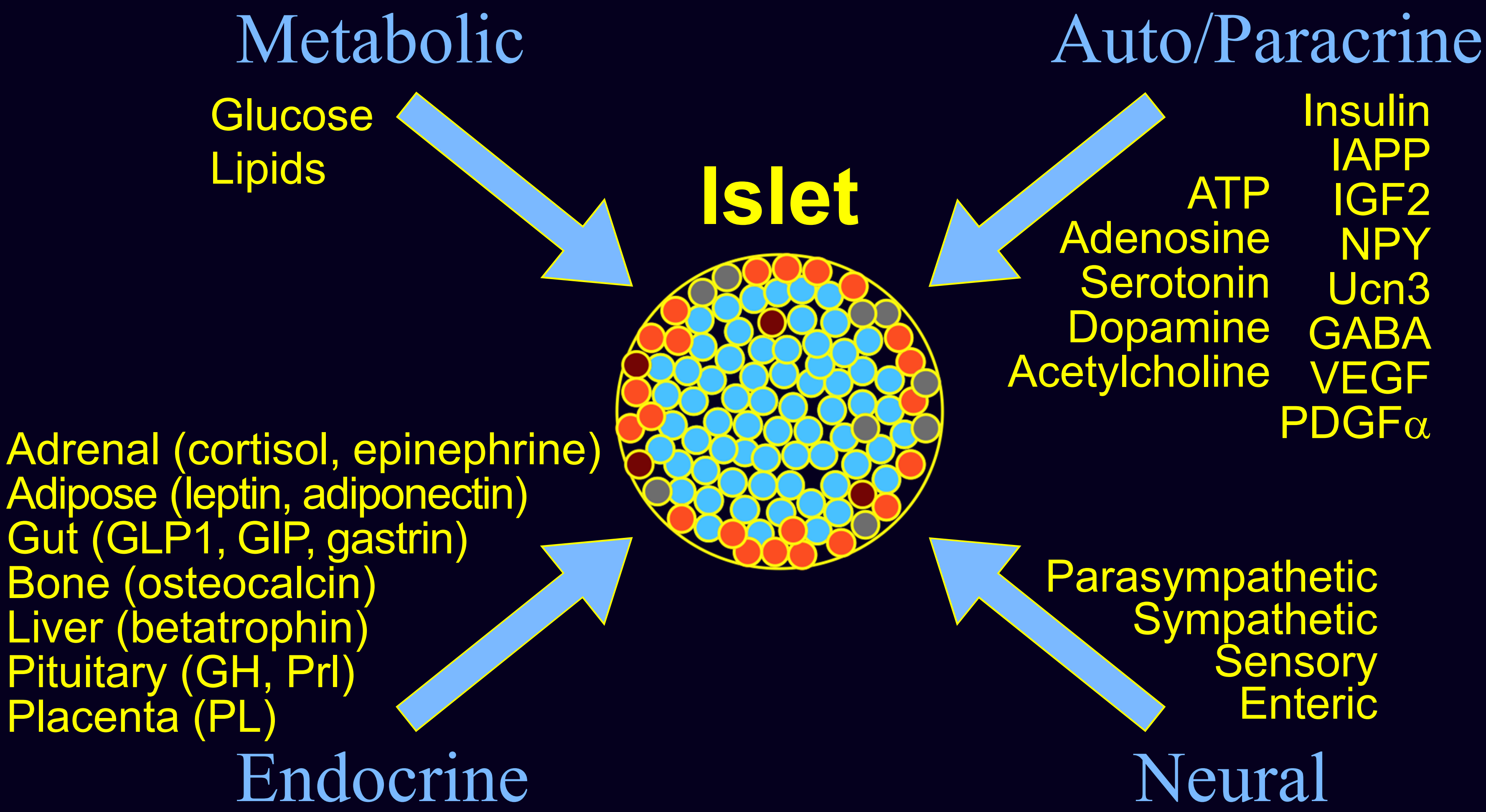
KAIST
- **Hail Kim**

UT Southwestern:
- Kathleen McGlynn
- **Melanie Cobb**

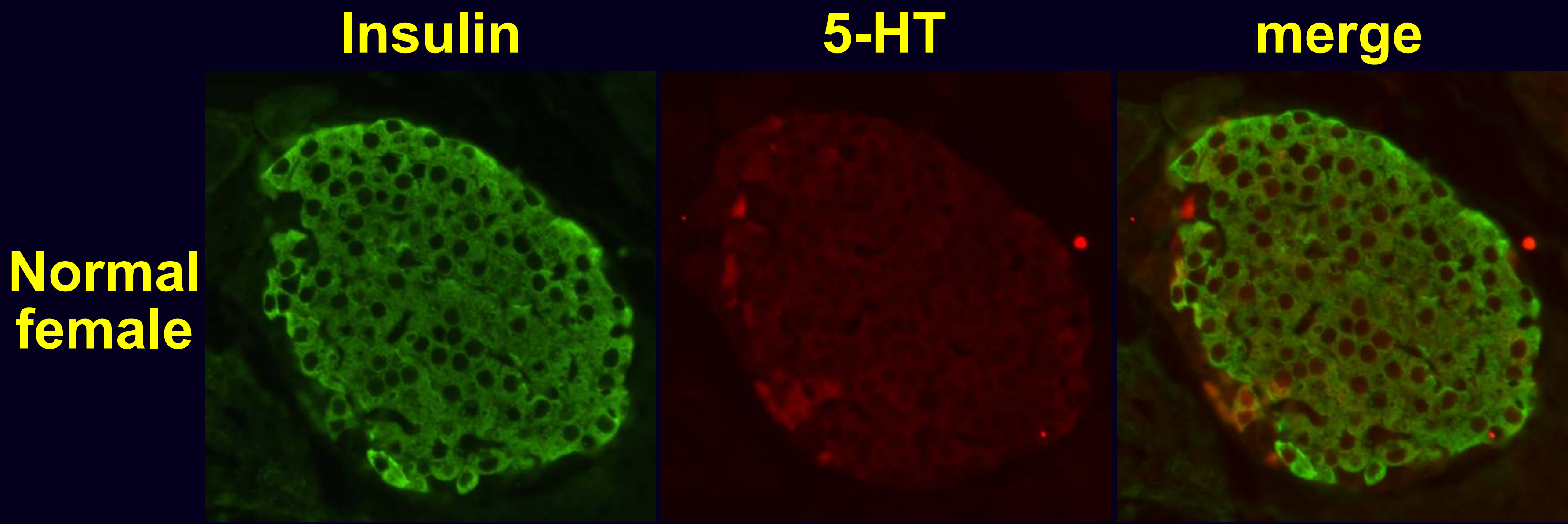
Kyorin University:
- Mica Ohara-Imaizumi
- **Shinya Nagamatsu**

Juntendo University
- Yukiko Toyofuku
- **Hirotaka Watada**
- **Takeshi Miyatsuka**

β Cell Proliferation: Signals



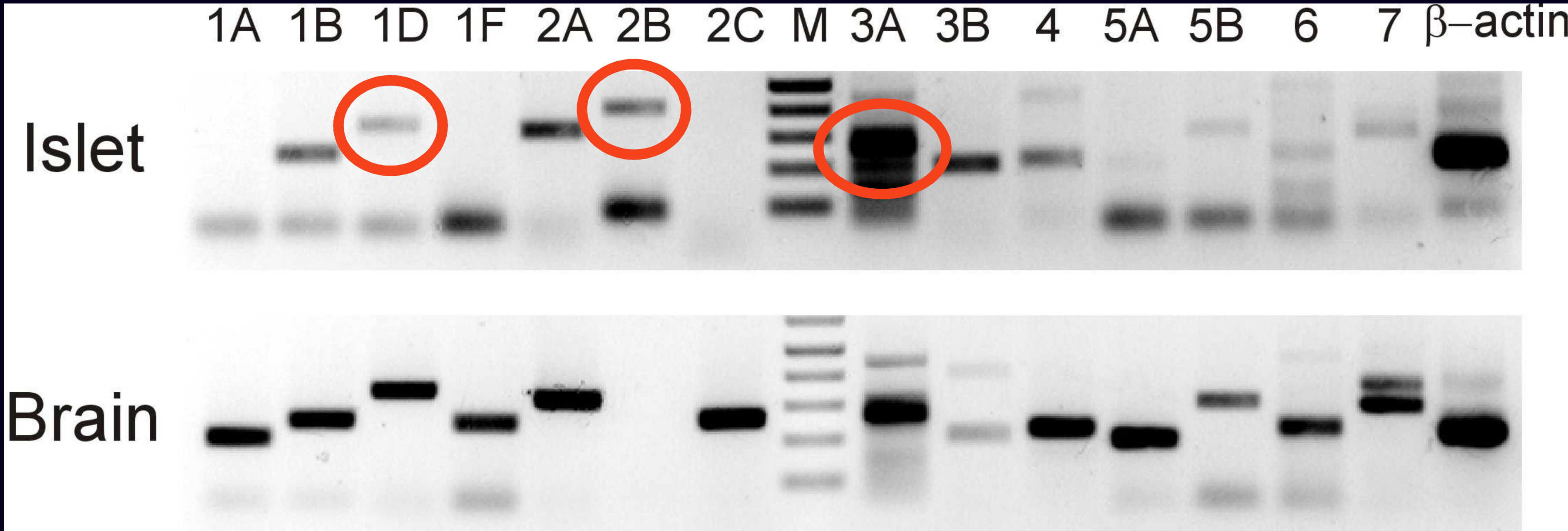
Serotonin (5-HT) in mouse islets



Nina Kishimoto

5-HT Receptors in the Islet

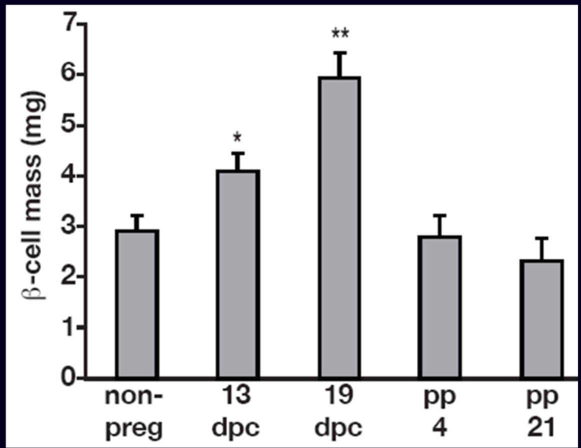
β-cell-specific expression

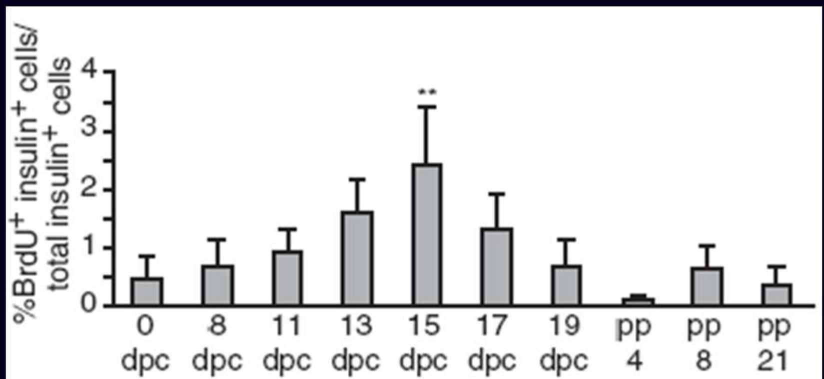


$G\alpha_i$ $G\alpha_q$ Ligand-gated cation channel

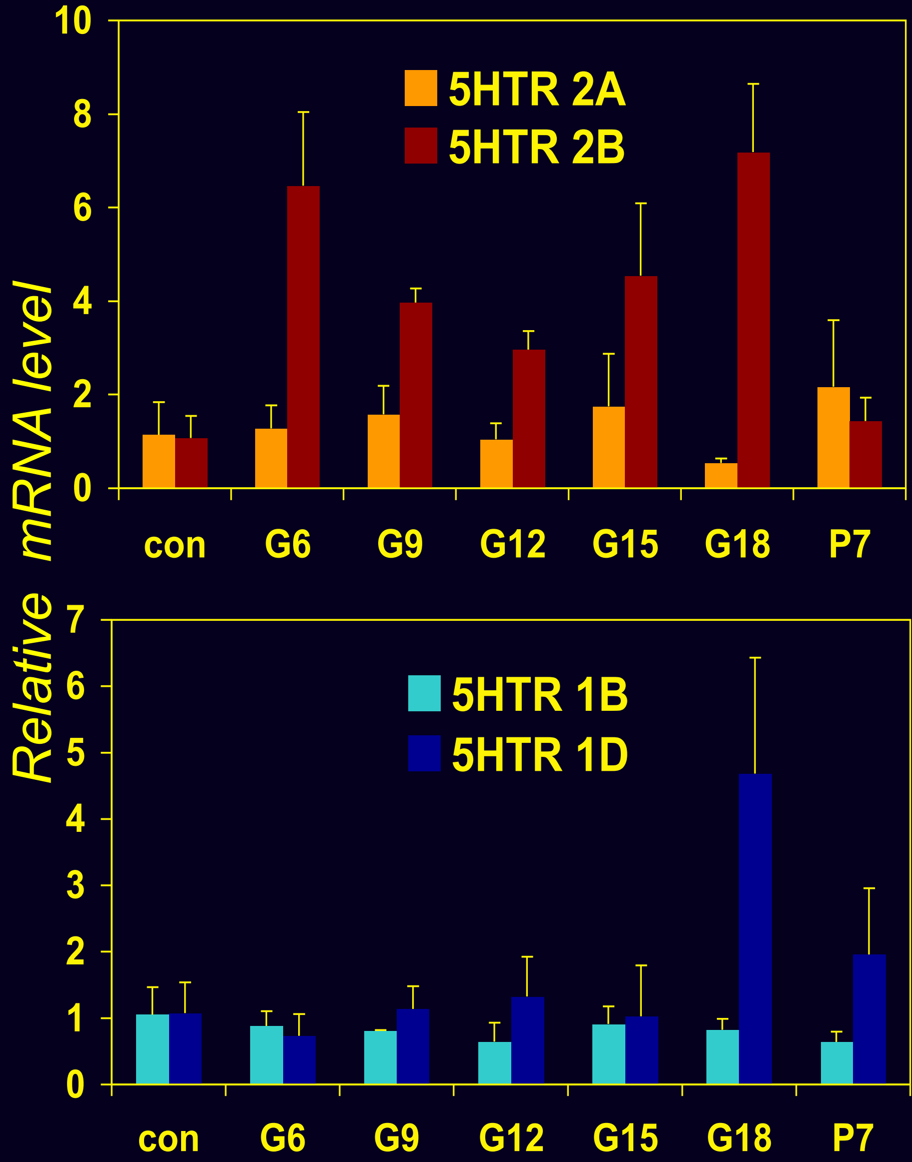
Ha-il Kim

5-HTR in islets during pregnancy



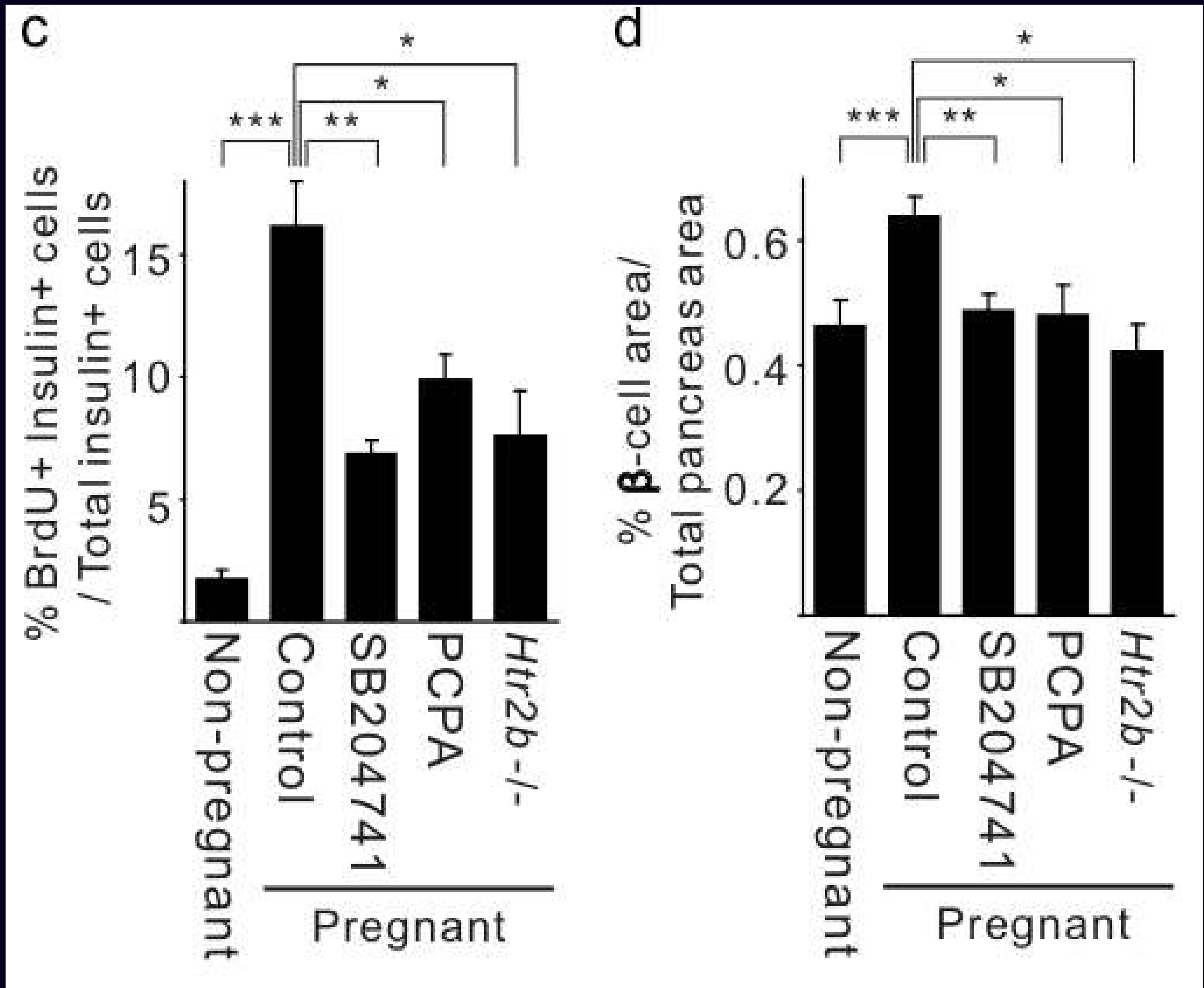


Karnik, et al., 2007



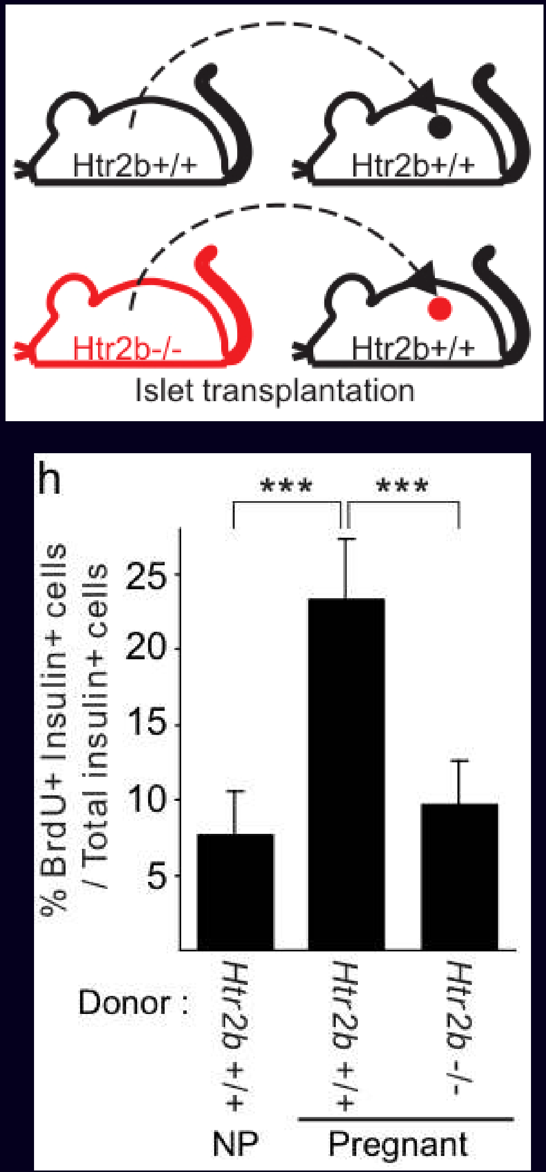
Ha-il Kim

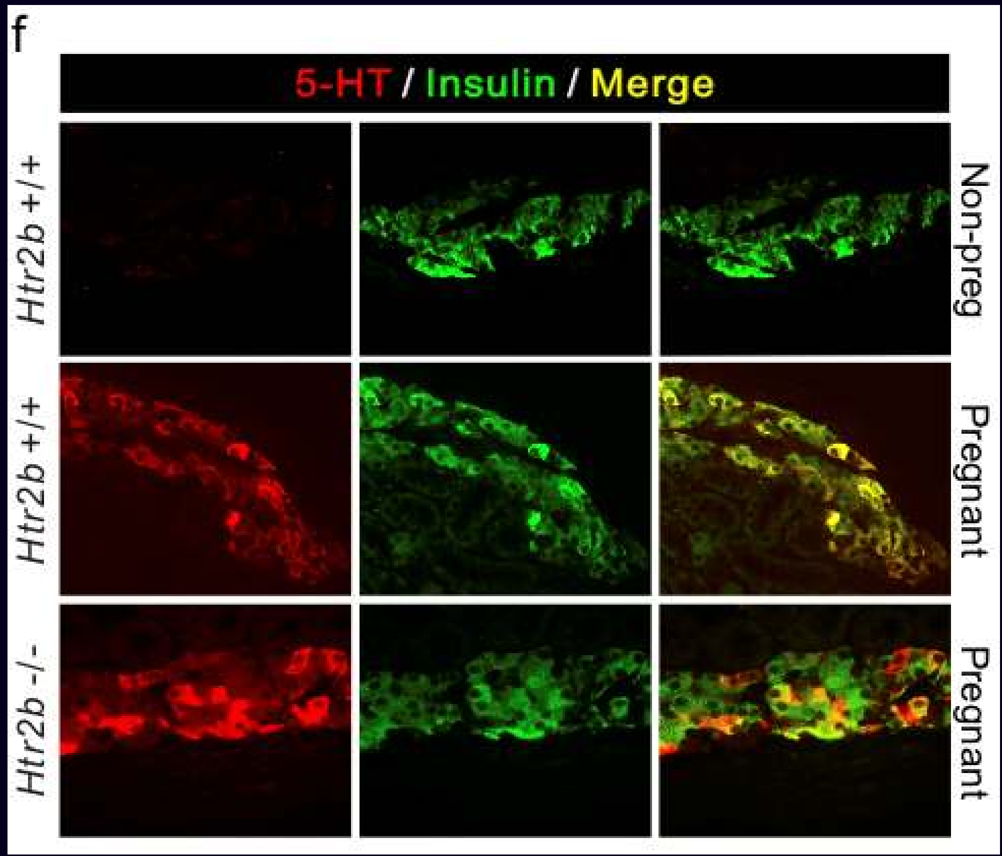
5-HT receptor inhibitor



Ha-il Kim

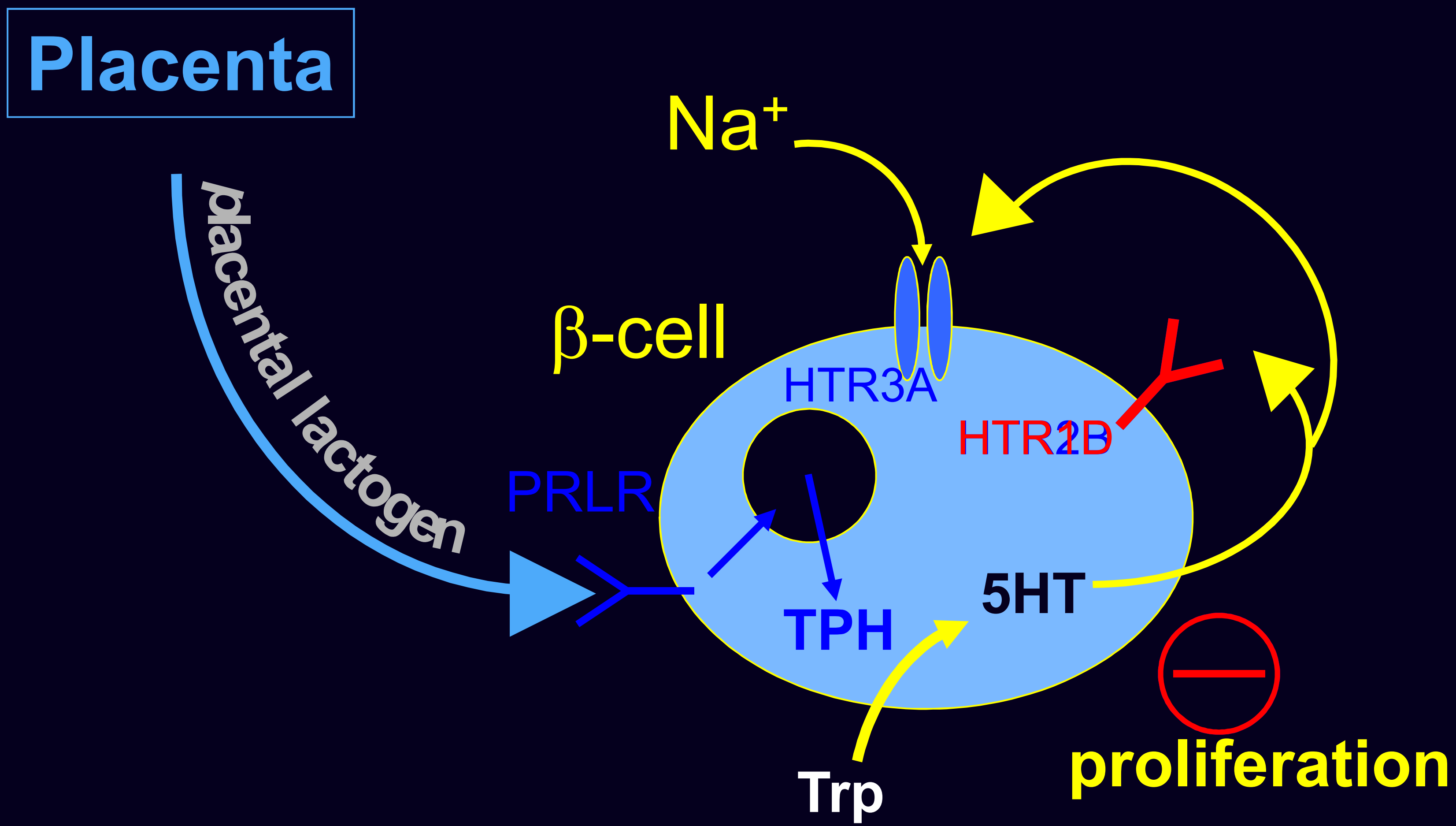
Htr2b KO Islets





Ha-il Kim

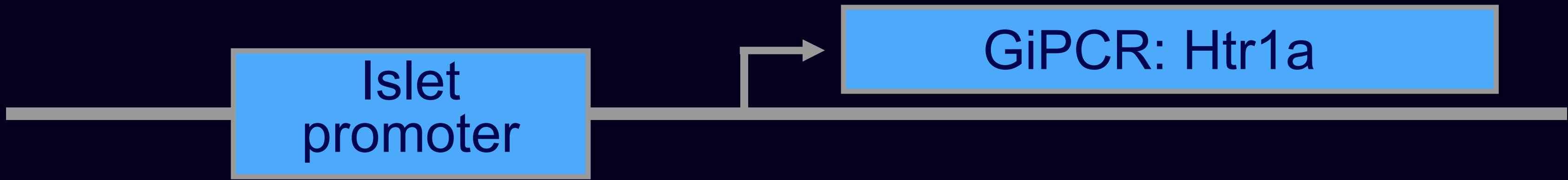
β-cell Population in Pregnancy



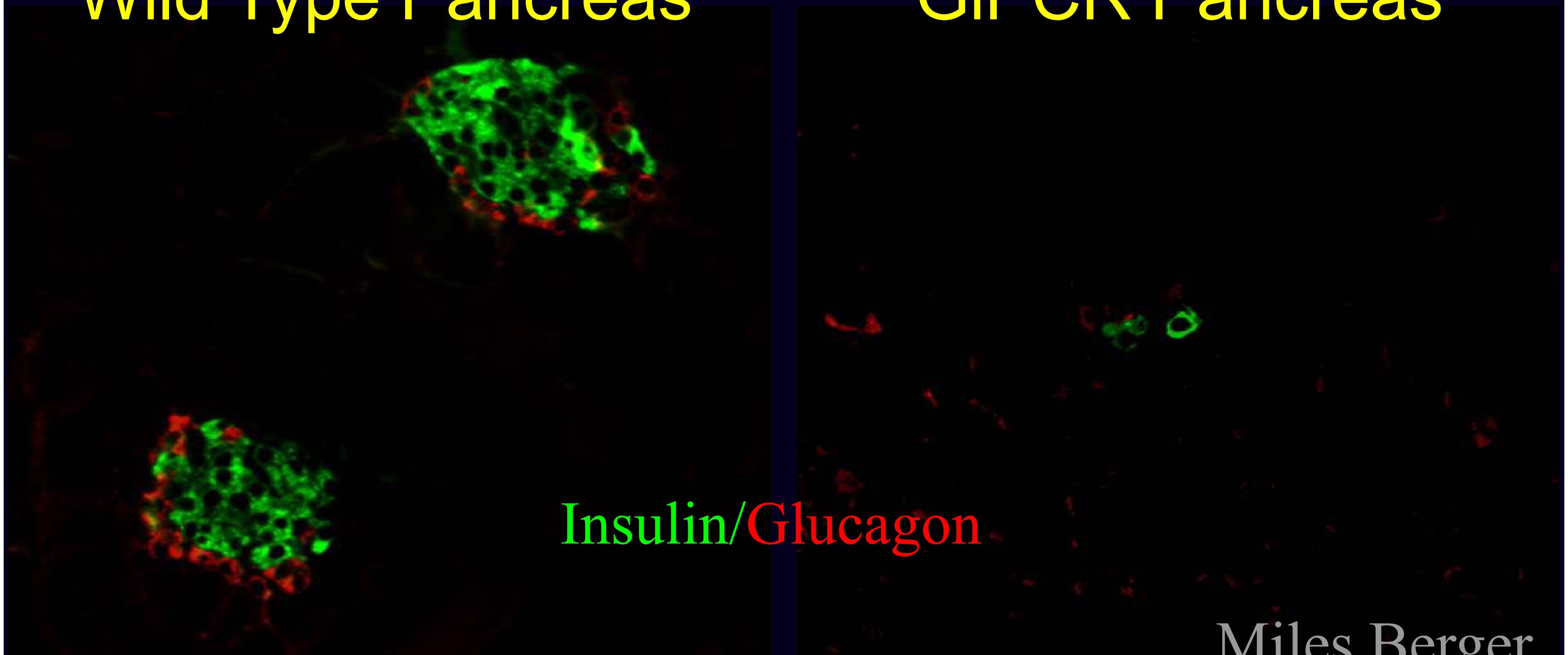
GPCRs Implicated in β-Cell Proliferation

A. $G\alpha_{q/11}$-linked:	Chrm3 Htr2b
B. $G\alpha_s$-linked:	Glp1r Gipr Adora2b
C. $G\alpha_{12/13}$-linked:	?
D. $G\alpha_{i/o}$-linked:	Htr1d?

$G\alpha_{i/o}$ Signaling: Increased



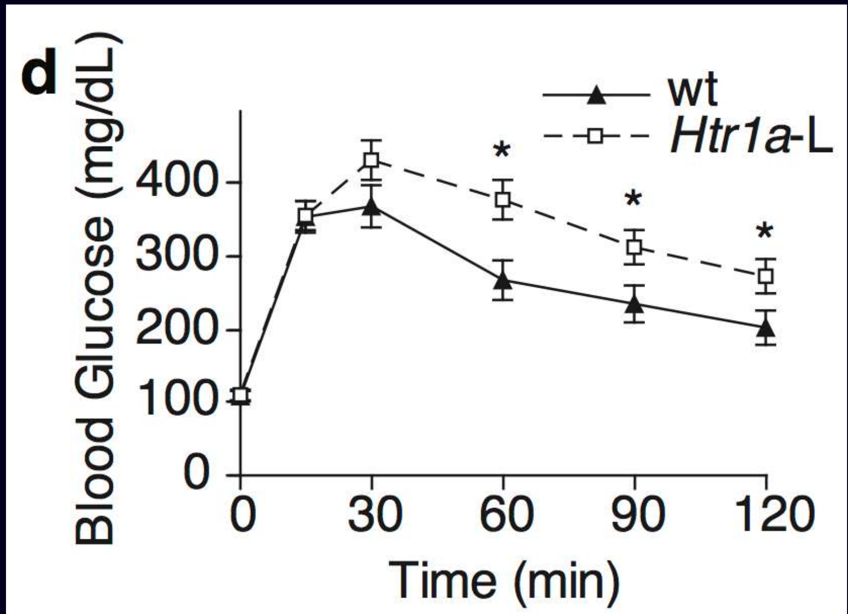
Wild Type Pancreas | GiPCR Pancreas

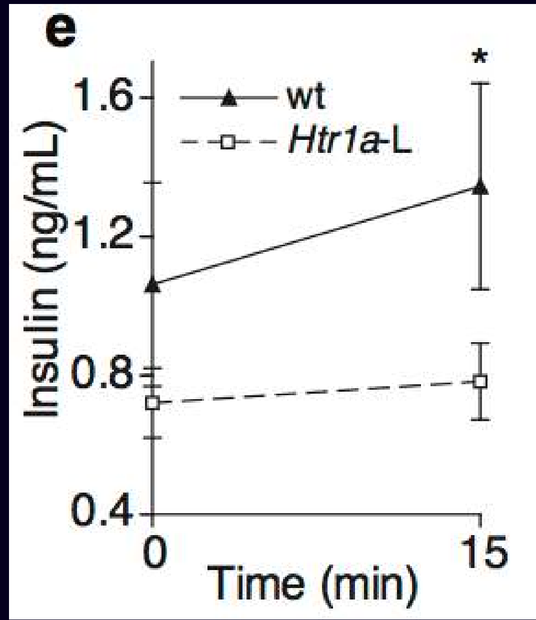


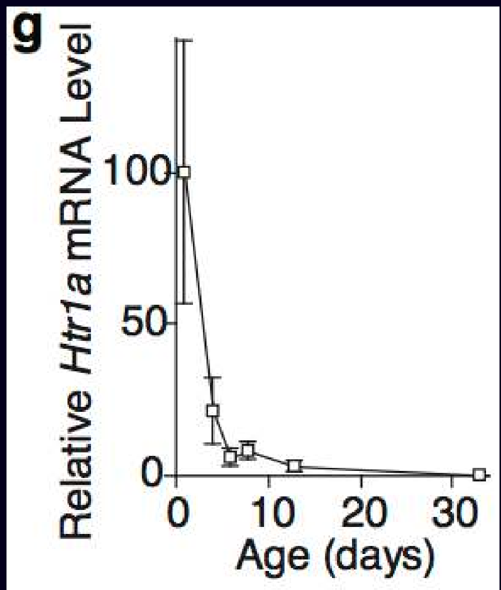
Insulin/Glucagon

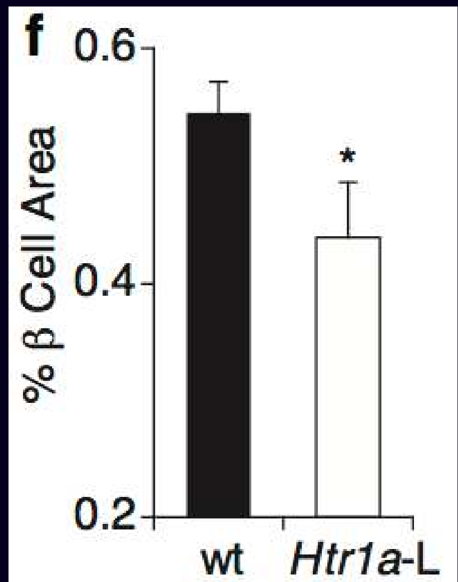
Miles Berger
Larry Tecott

$G\alpha_{i/o}$ Signaling: Increased



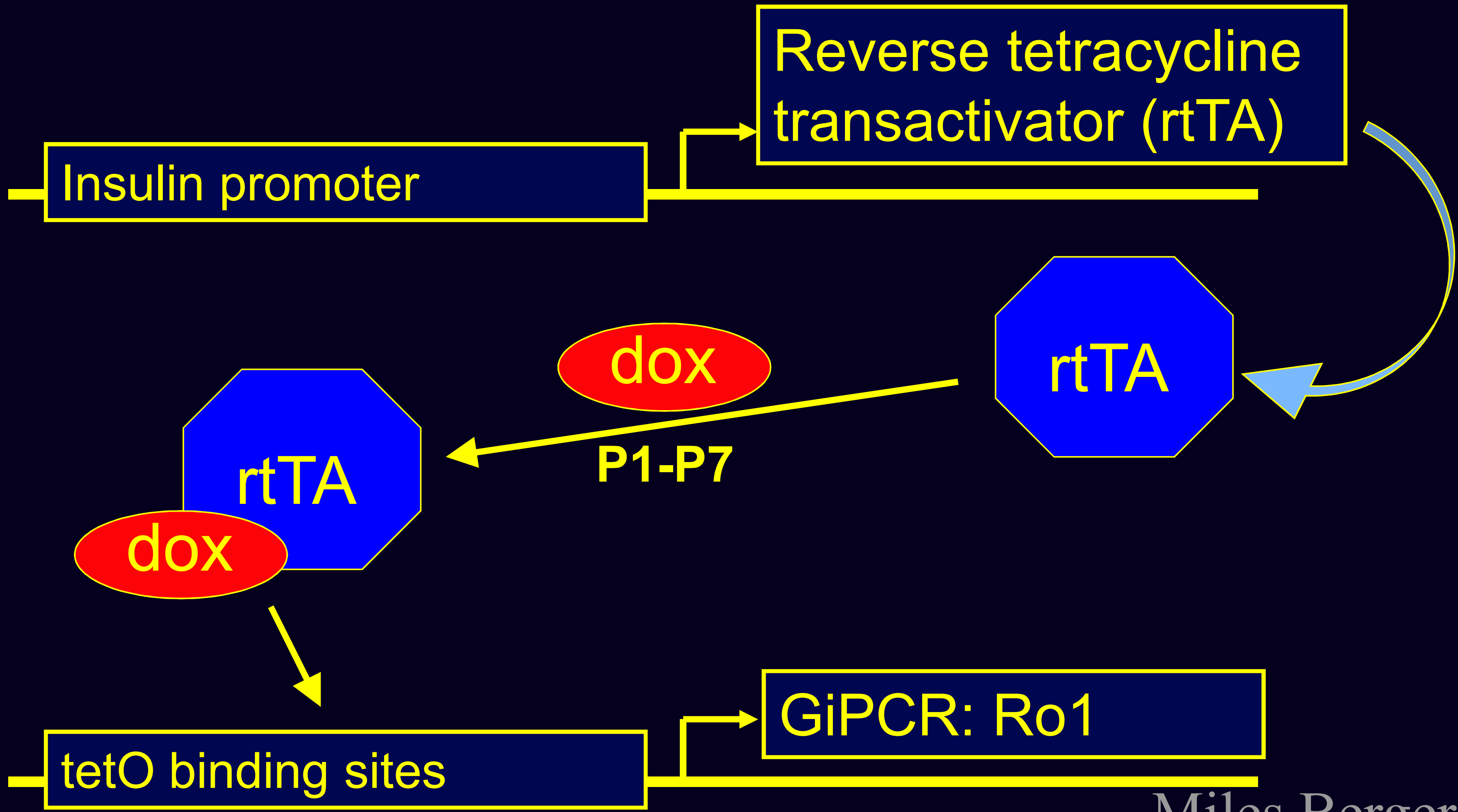






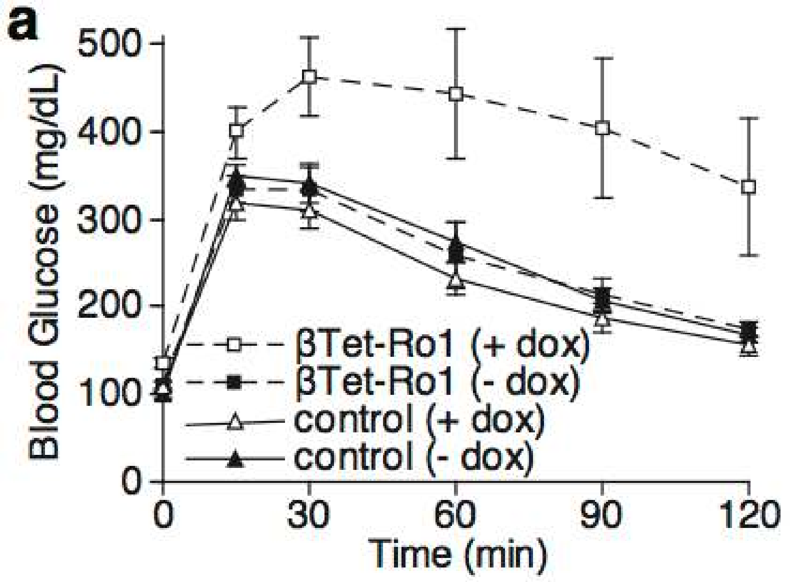
Miles Berger
Larry Tecott

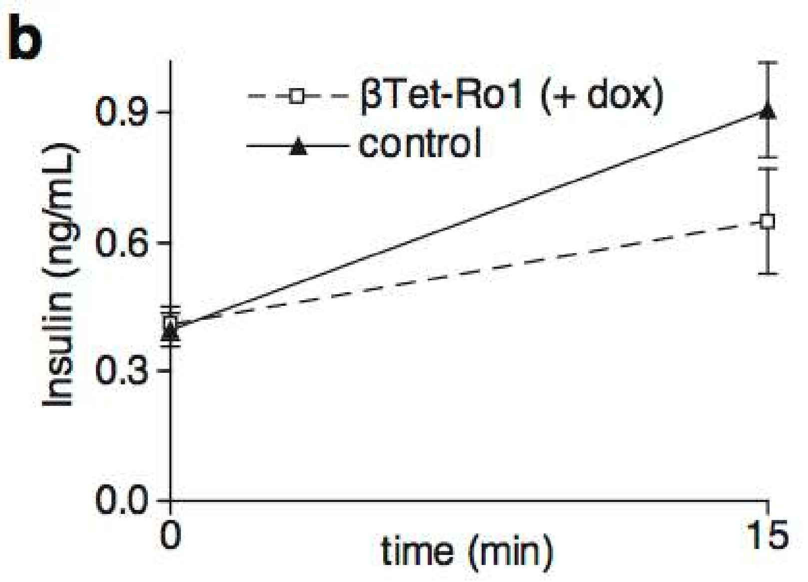
$G\alpha_{i/o}$ Signaling: Increased

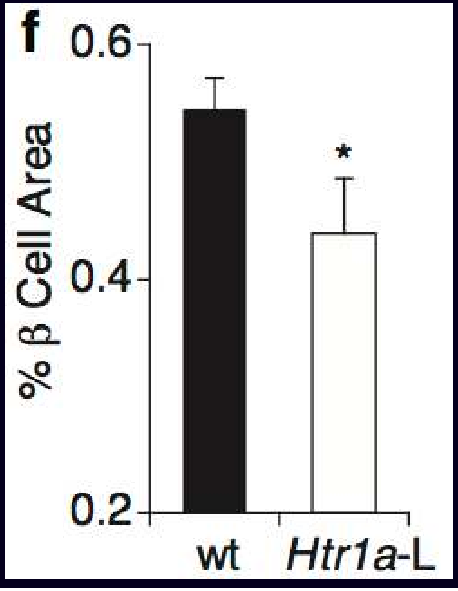


Miles Berger
Larry Tecott

$G\alpha_{i/o}$ Signaling: Increased

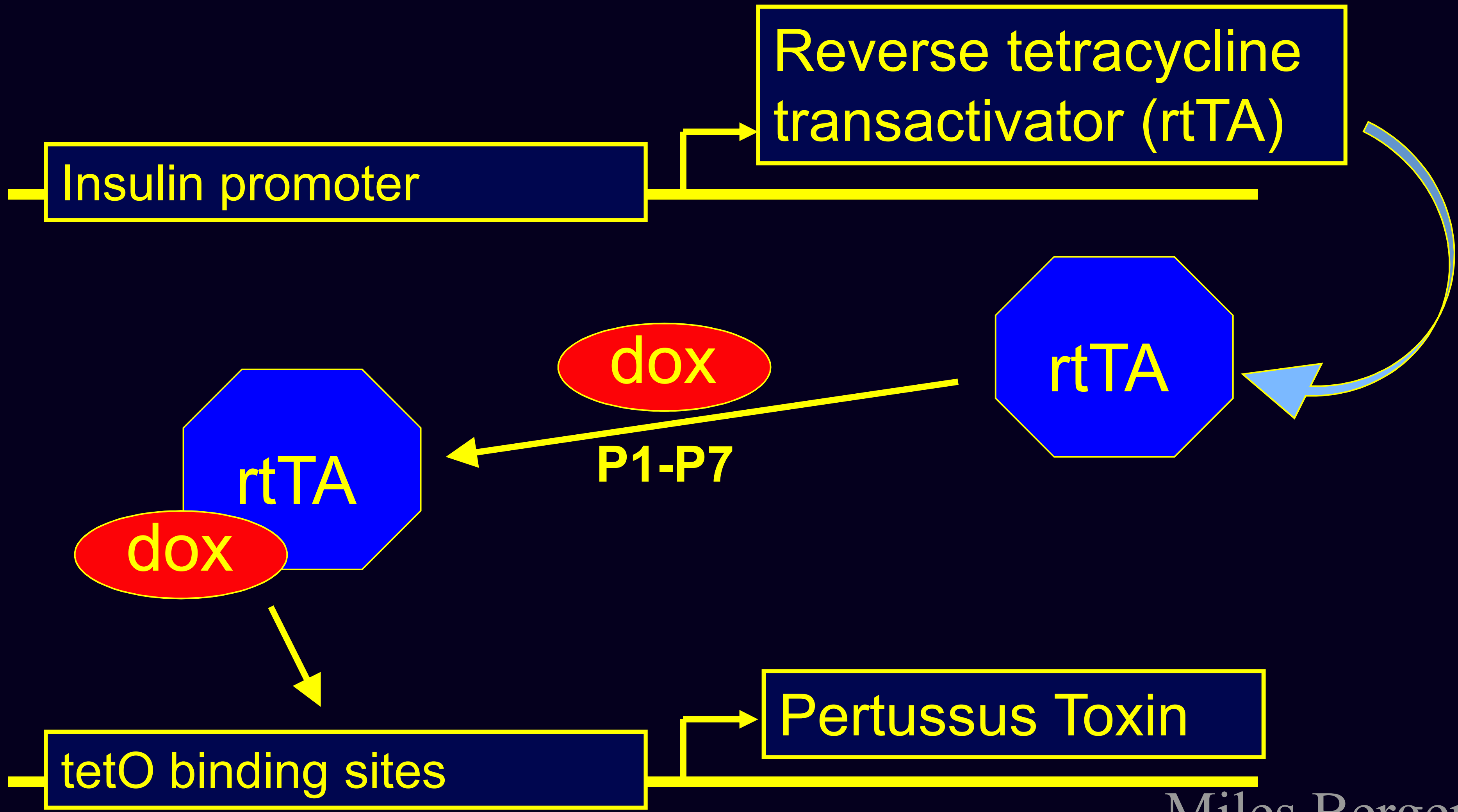






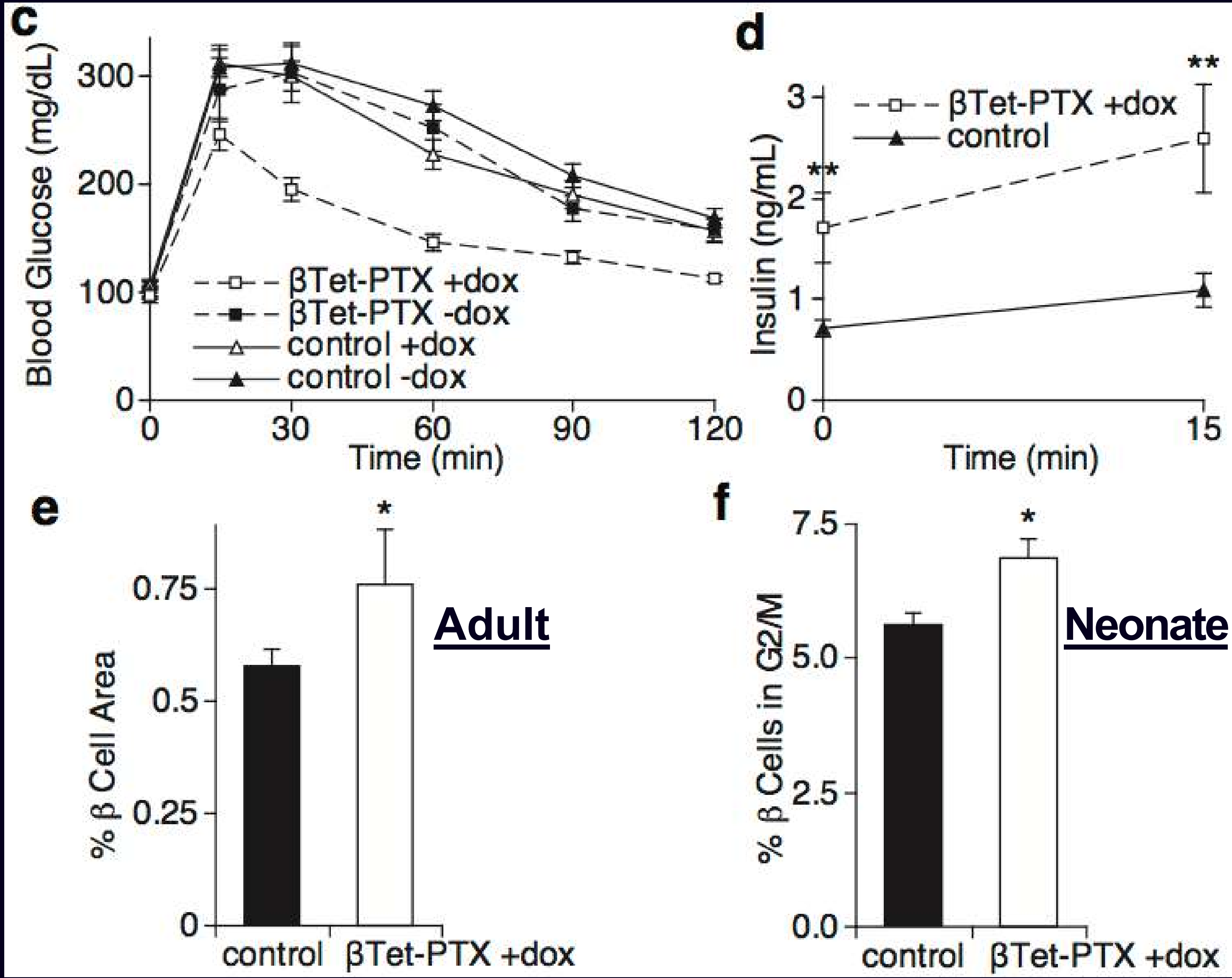
Miles Berger
Larry Tecott

Gα$_{i/o}$ Signaling



Miles Berger
Larry Tecott

$G\alpha_{i/o}$ Signaling: Decreased



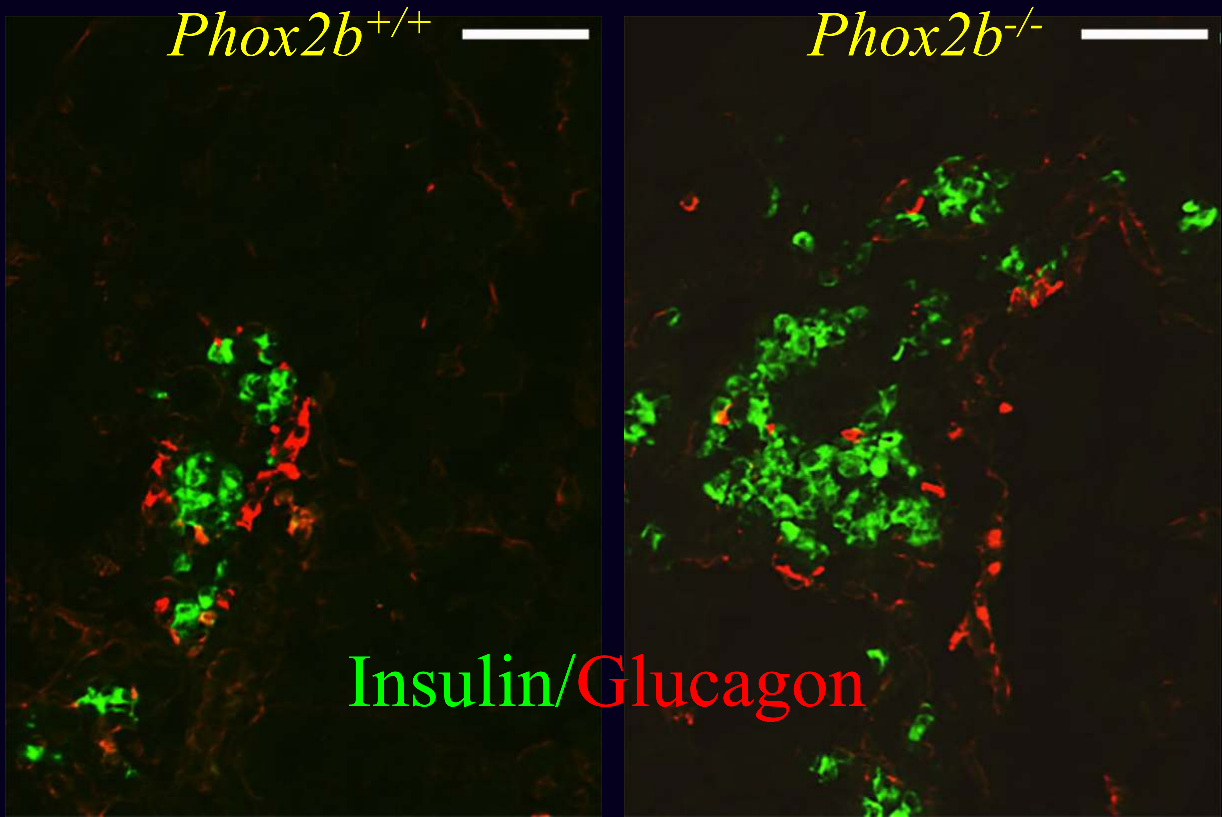
Miles Berger
Larry Tecott

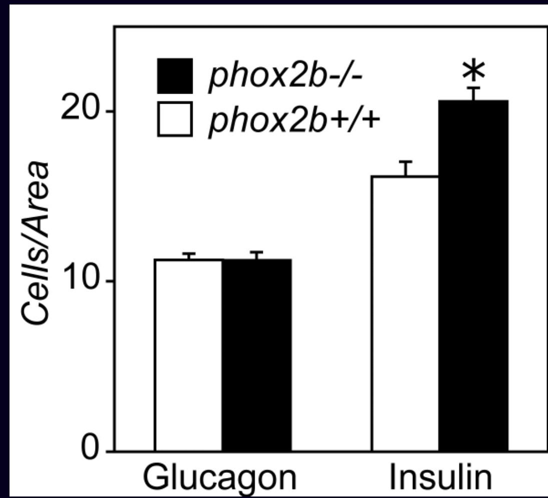
β-cell $G\alpha_{i/o}$ Receptors

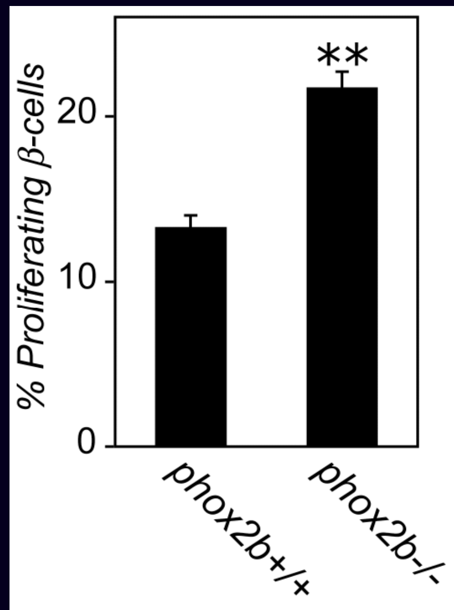
Gαi/o-linked GPCR Genes in β Cells			
Gene	E18.5 by RT-PCR		Adult RPKM
	Mean	SEM	
Cxcr6	63.17	21.52	0.20
Adra2a	22.67	4.80	58.67
Gabbr2	10.17	2.94	15.98
Aplnr	6.29	0.74	0.12
Galr1	4.91	1.55	16.51
Ccr9	4.60	1.65	0.030
Adora1	3.53	0.43	1.27
Sstr3	2.78	0.28	44.56
Gpr19	2.74	0.88	0.60
S1pr1	2.12	0.33	0.15
P2ry2	2.03	0.96	0.015
Niacr1	1.90	1.06	0.78
Gpr183	1.83	0.26	0.067
Gabbr1	1.66	0.45	4.06
Ednra	1.61	0.46	0.031
Ffar3	1.50	0.49	6.22
Ptger3	1.18	0.24	6.35
Casr	1.07	0.18	23.25

Greg Ku
Hail Kim
Takeshi Miyatsuka

Neural Regulation of β Cell Mass

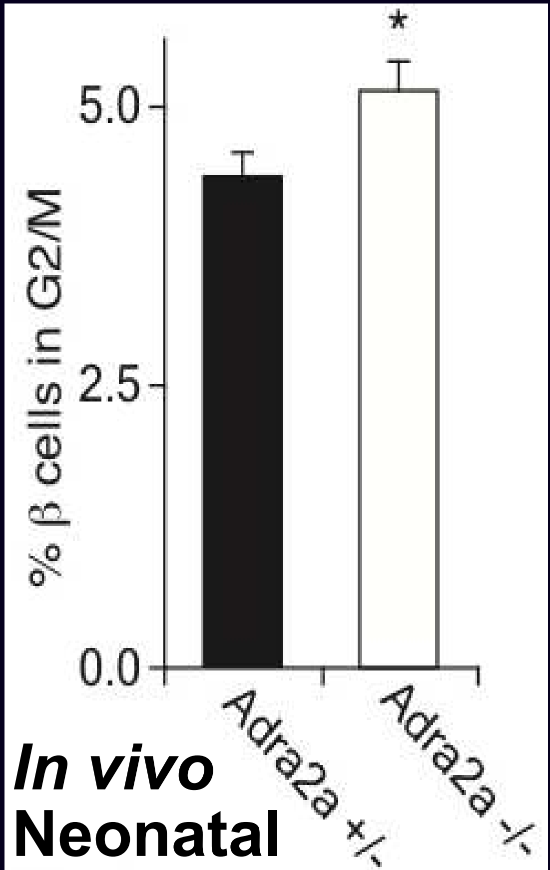




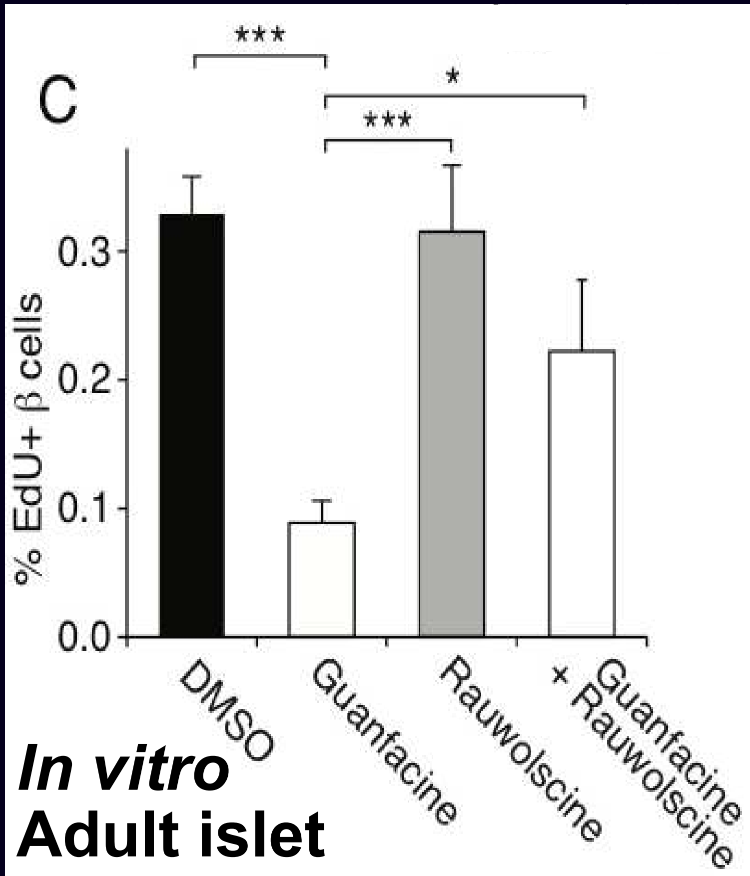


Nada Nekrep

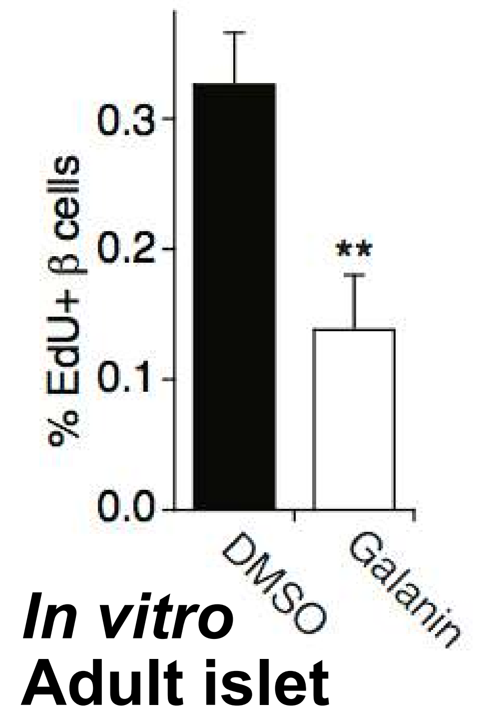
Sympathetic Signals Inhibit Proliferation



In vivo
Neonatal



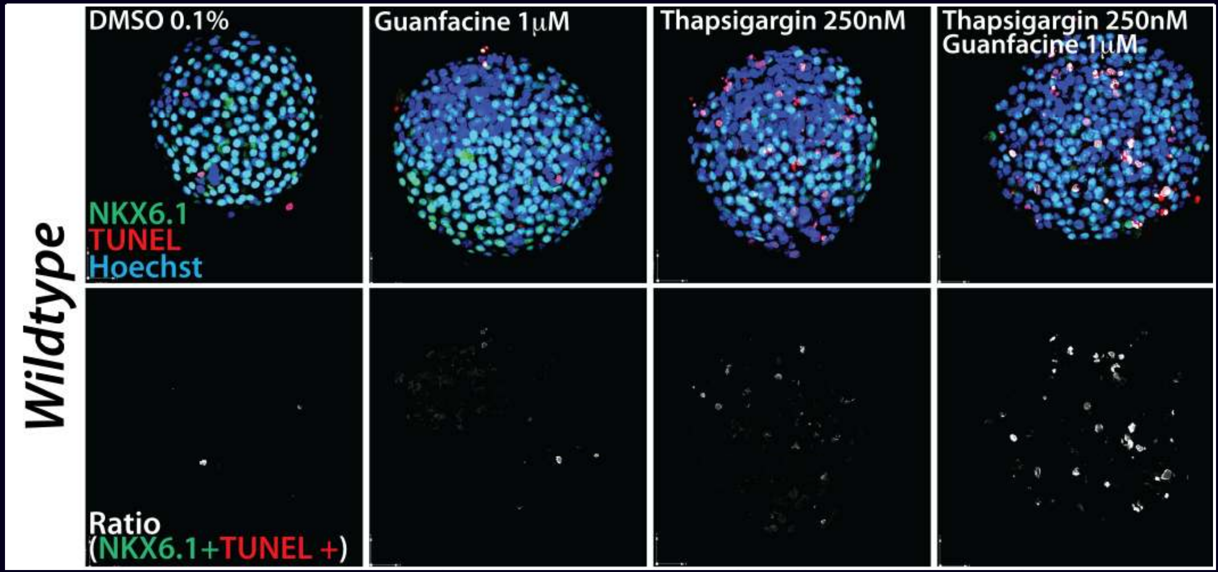
In vitro
Adult islet

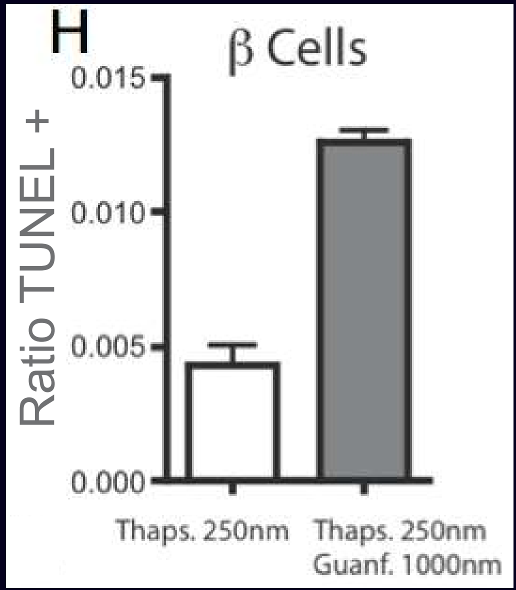


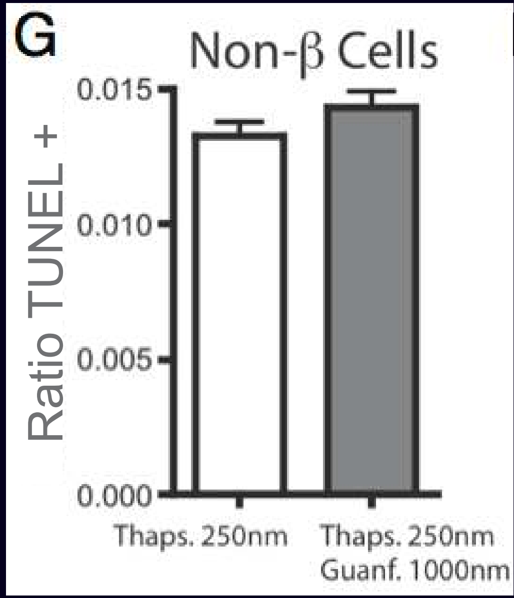
In vitro
Adult islet

Takeshi Miyatsuka Hector Macias

$G\alpha_{i/o}$ Signals Induce Apoptosis

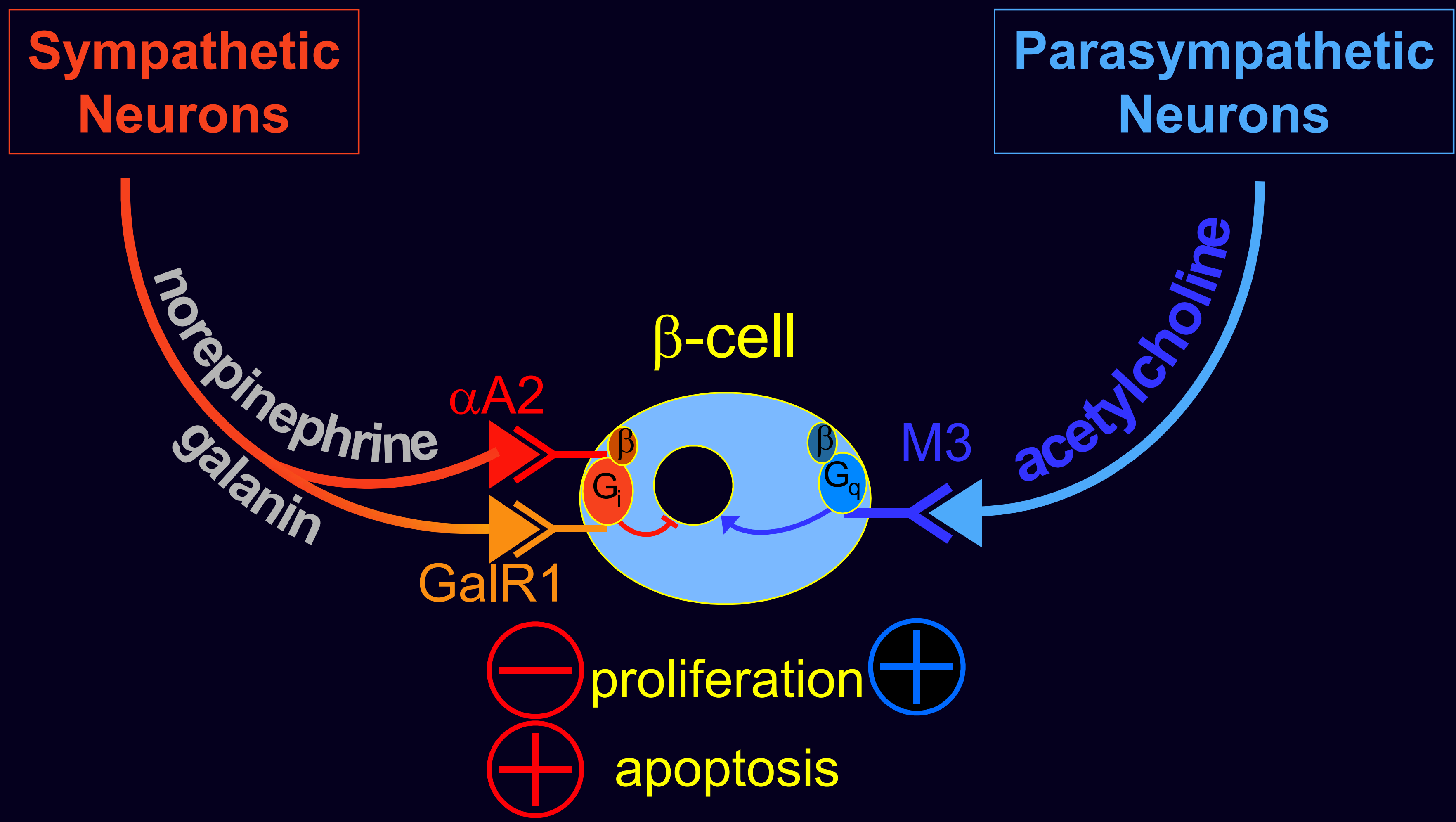




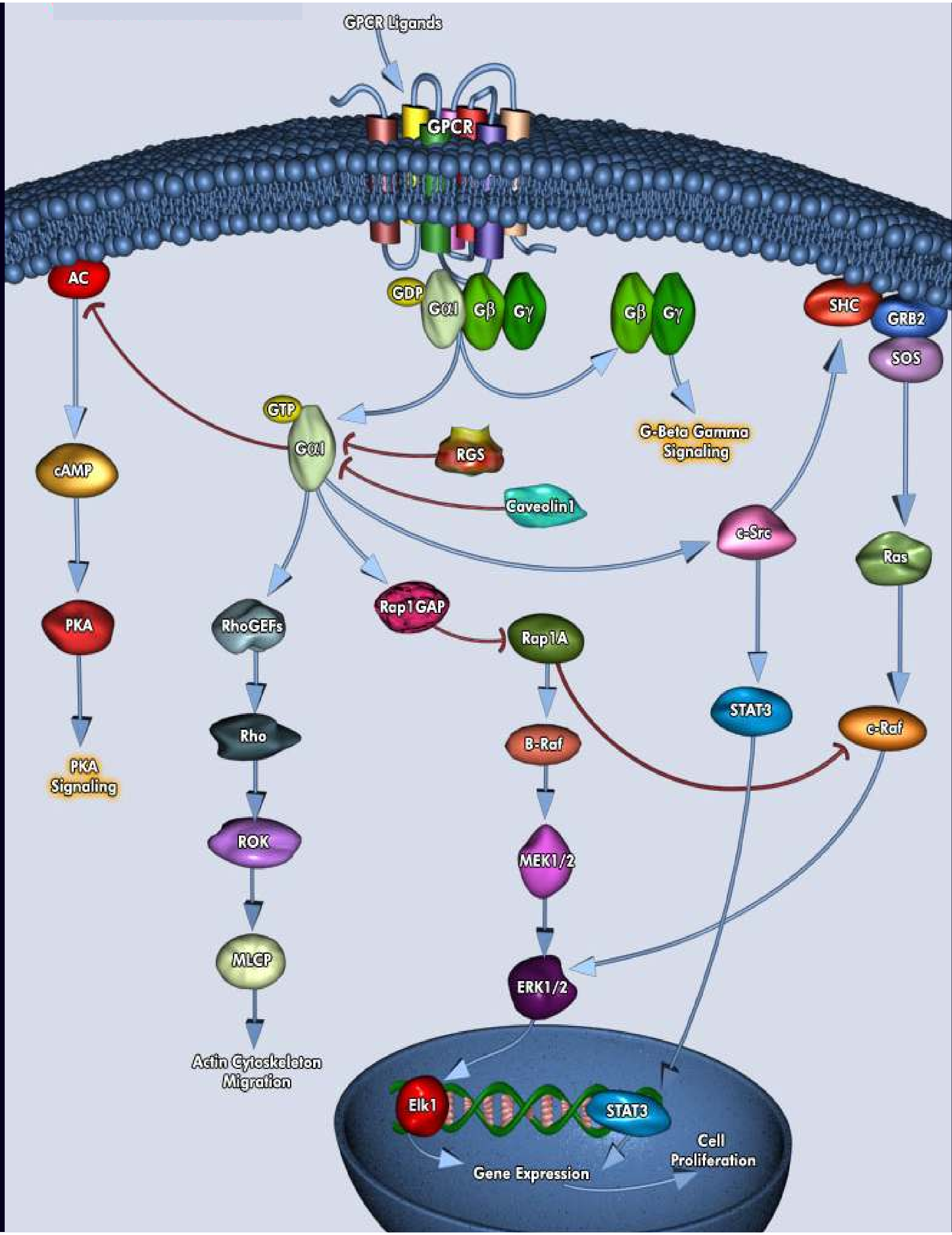


Hector Macias

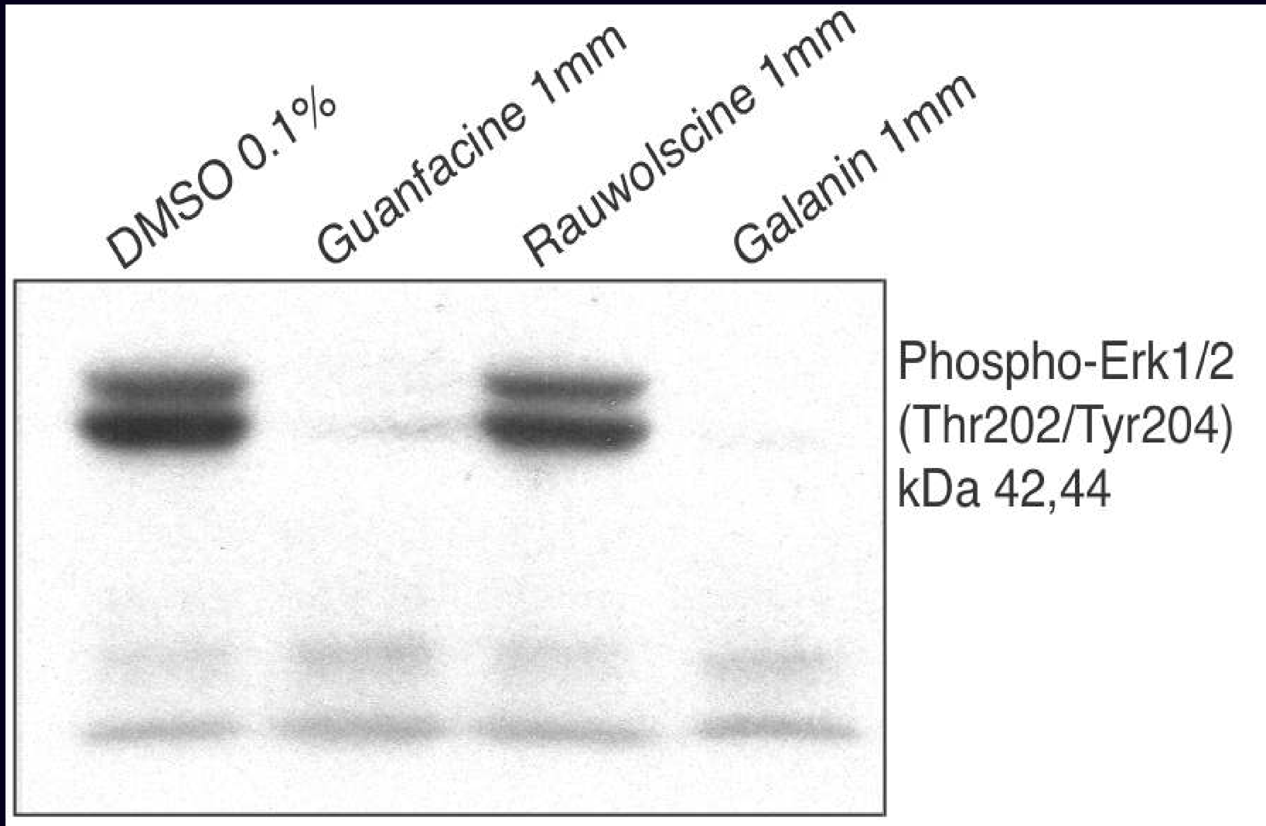
Neural Regulation of β-cell Proliferation

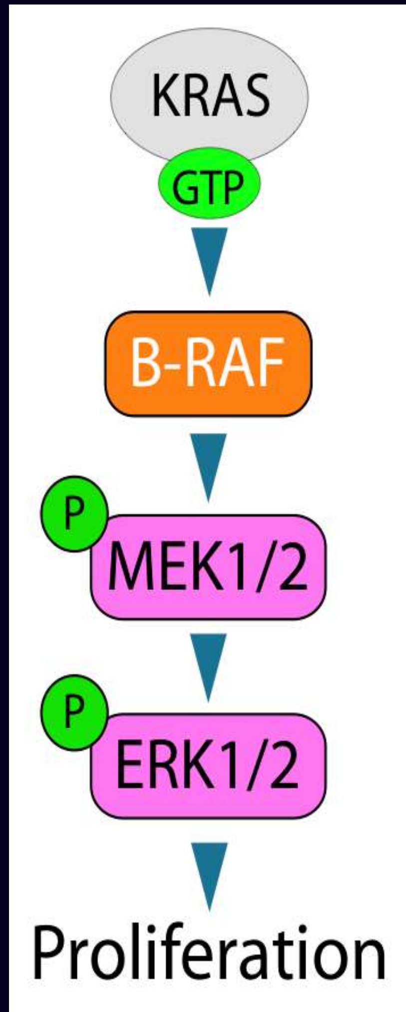


$G\alpha_{i/o}$ Signaling



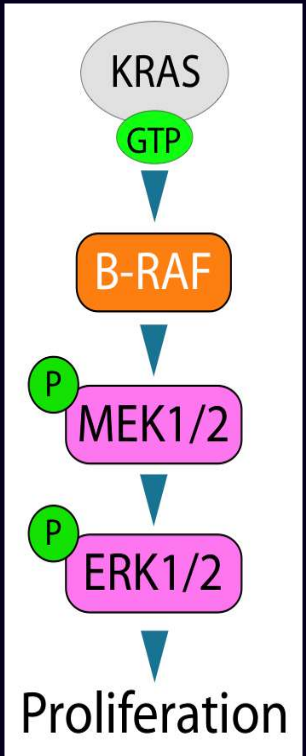
$G\alpha_{i/o}$ Signaling in the β Cell

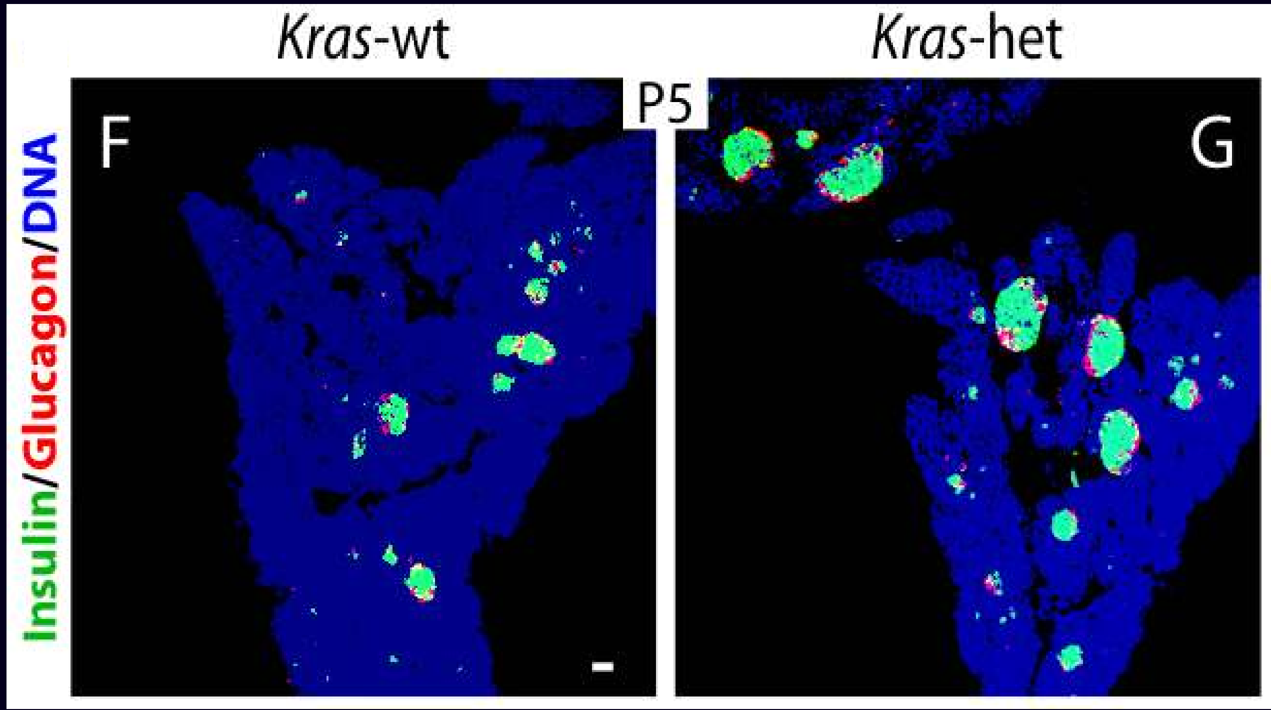


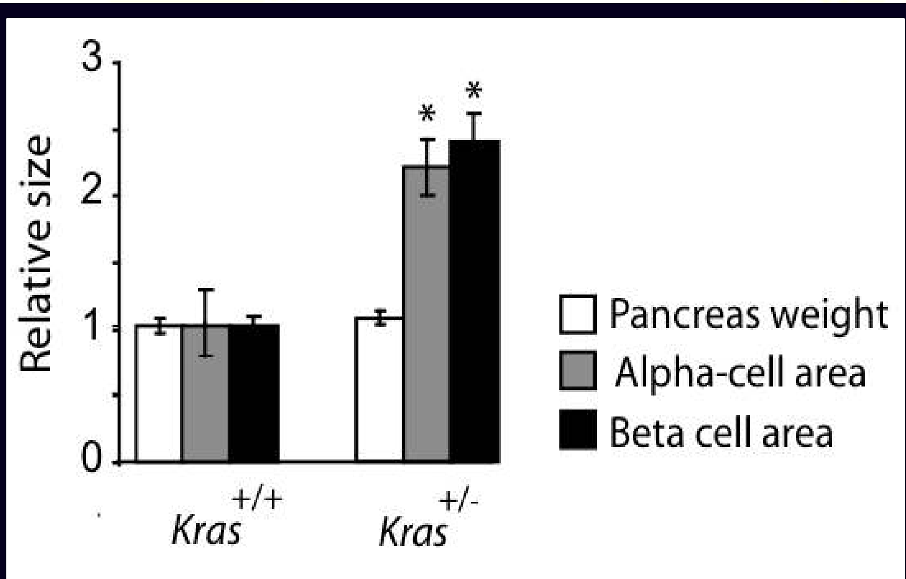


Hector Macias

K-Ras in the β Cell

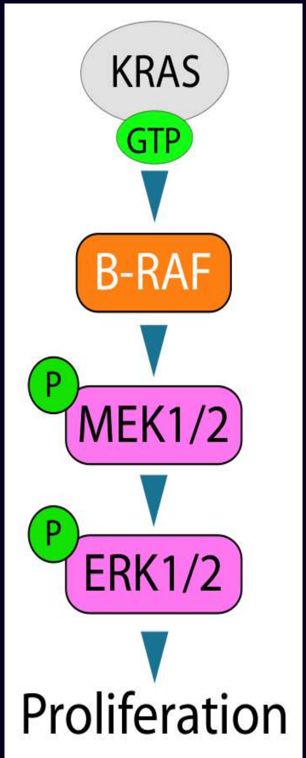


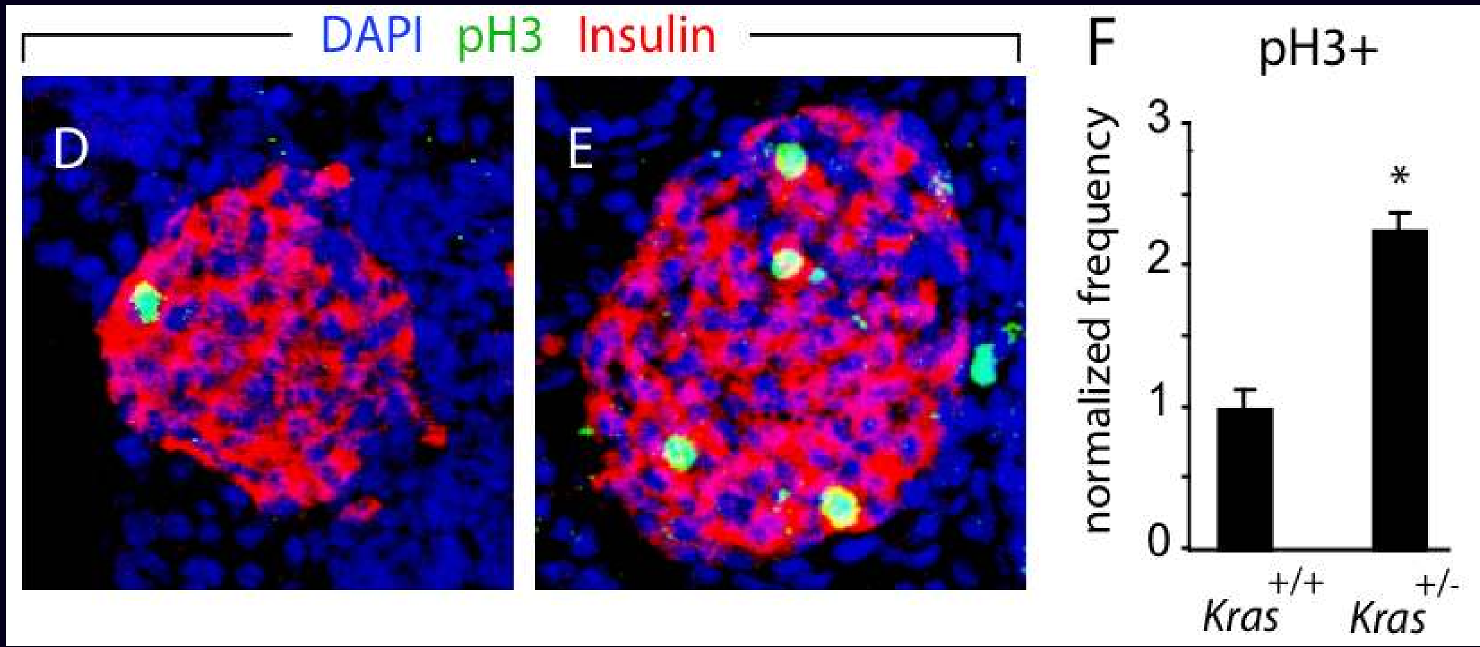




Chester Chamberlain

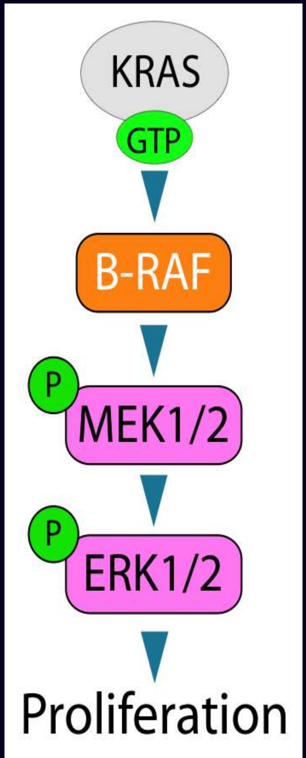
K-Ras in the β Cell

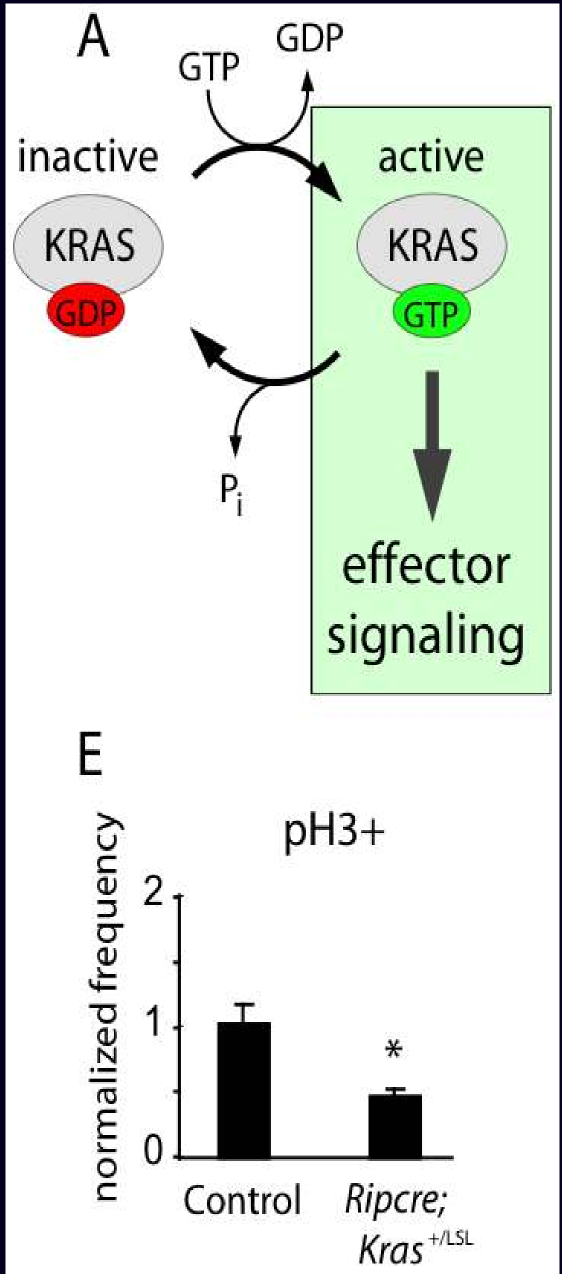


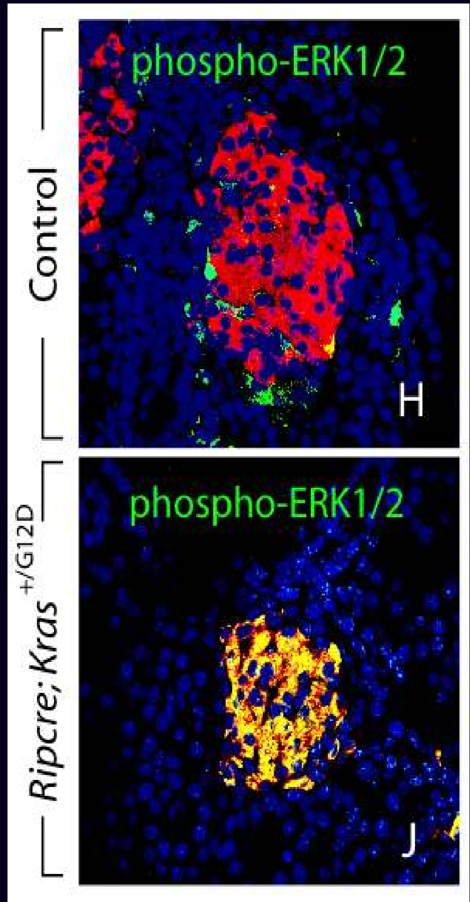


Chester Chamberlain

K-Ras in the β Cell

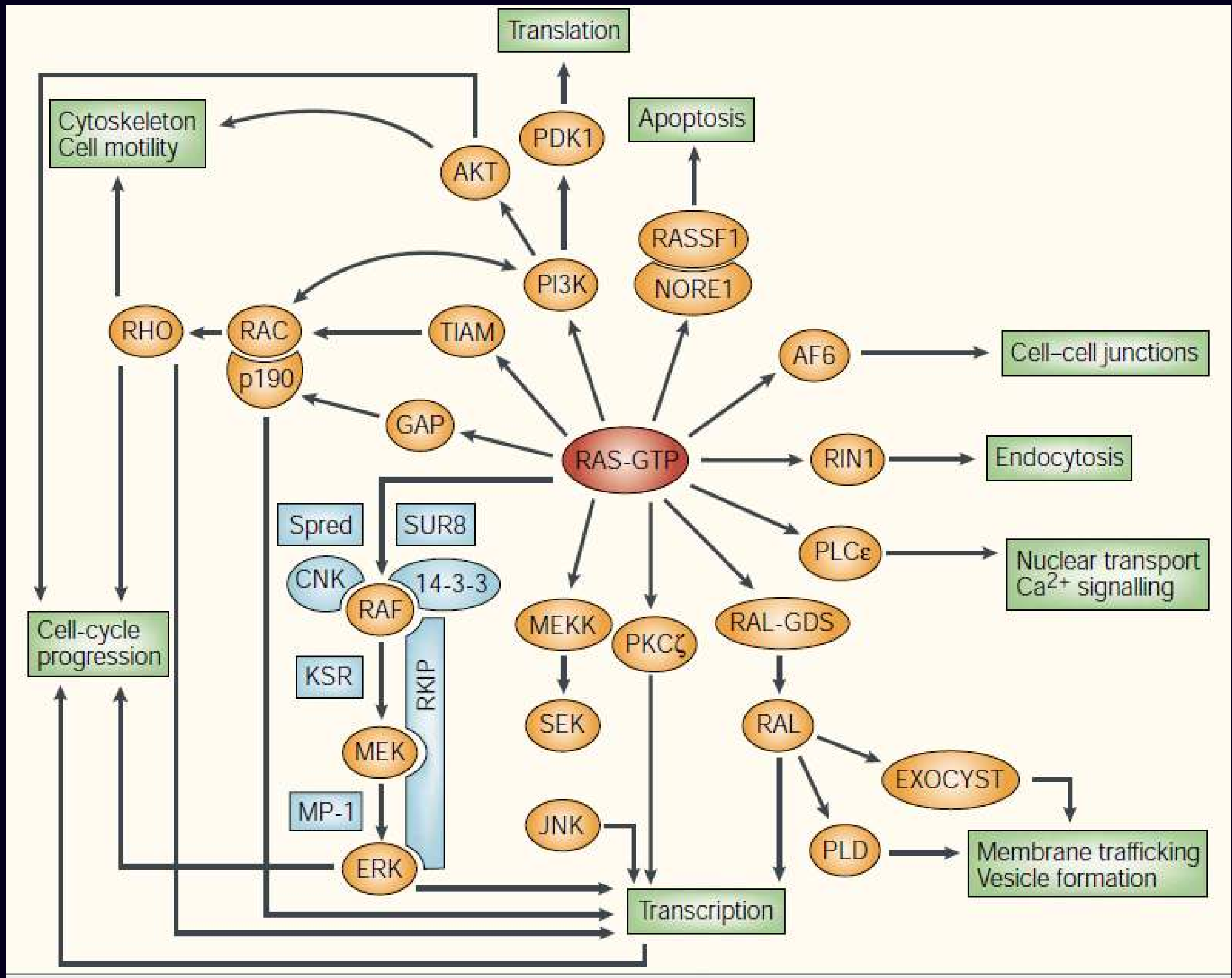






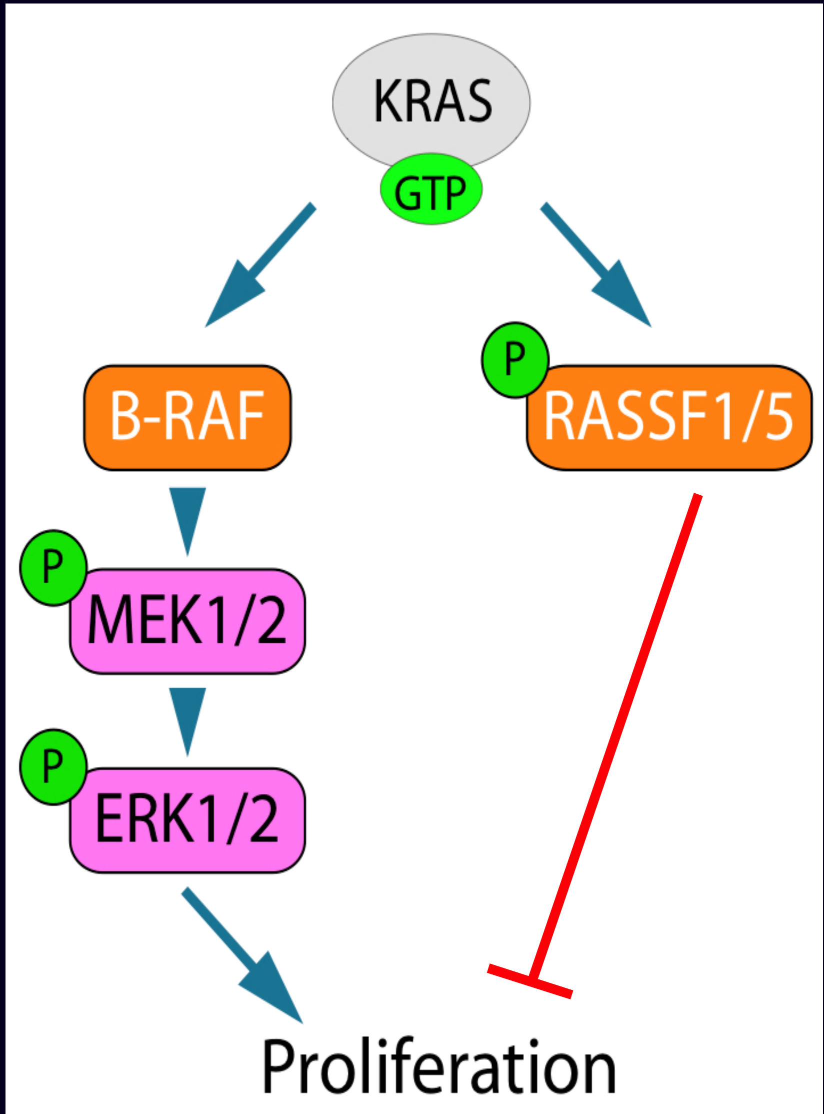
Chester Chamberlain

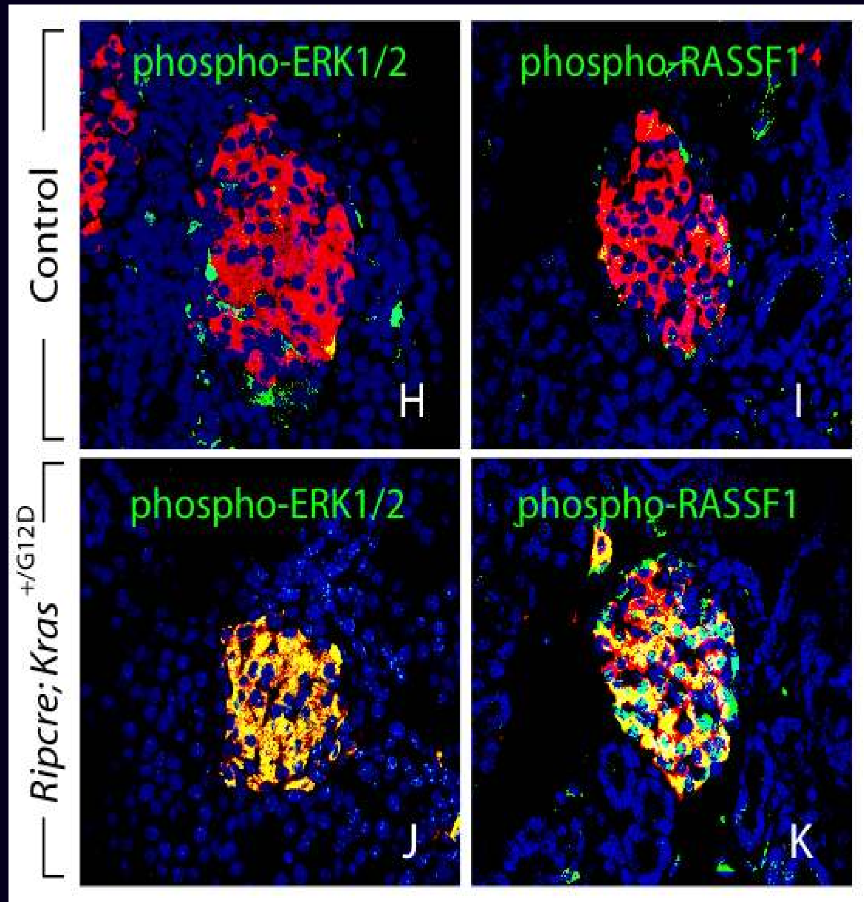
K-Ras activates diverse effector pathways



Malumbres and Barbacid, *Nature Reviews Cancer* 2002

K-Ras in the β Cell





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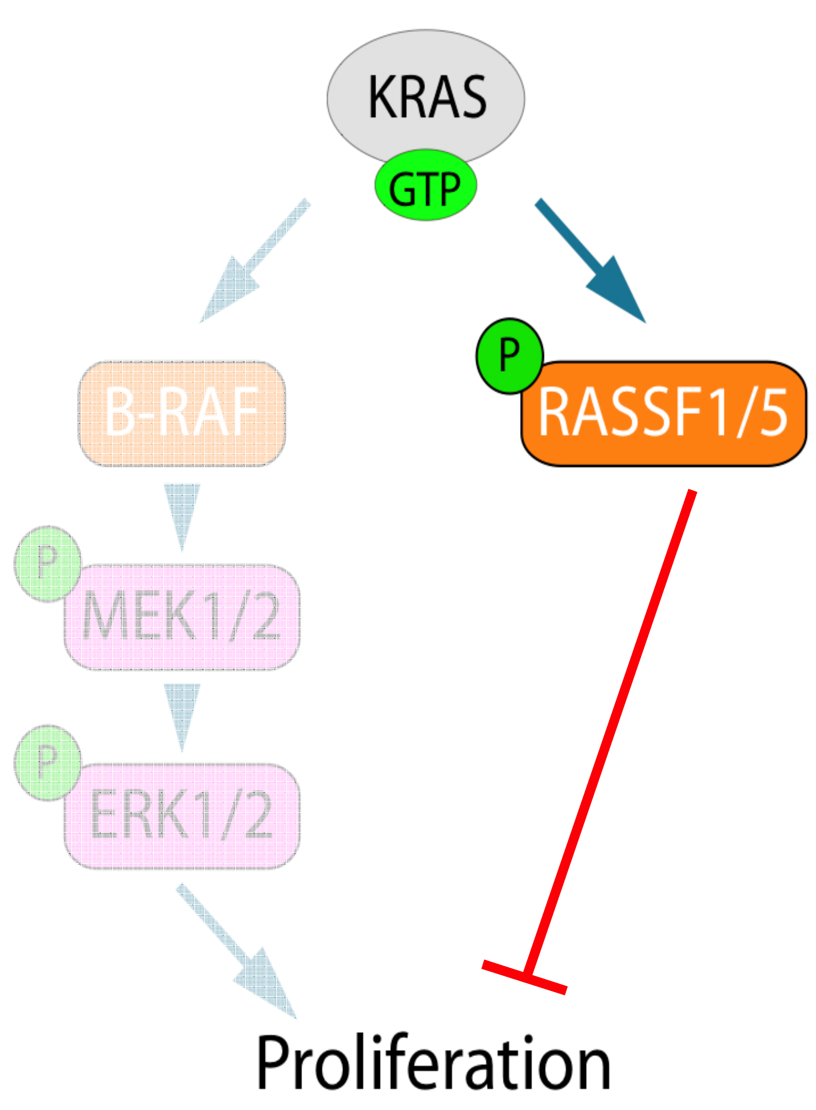
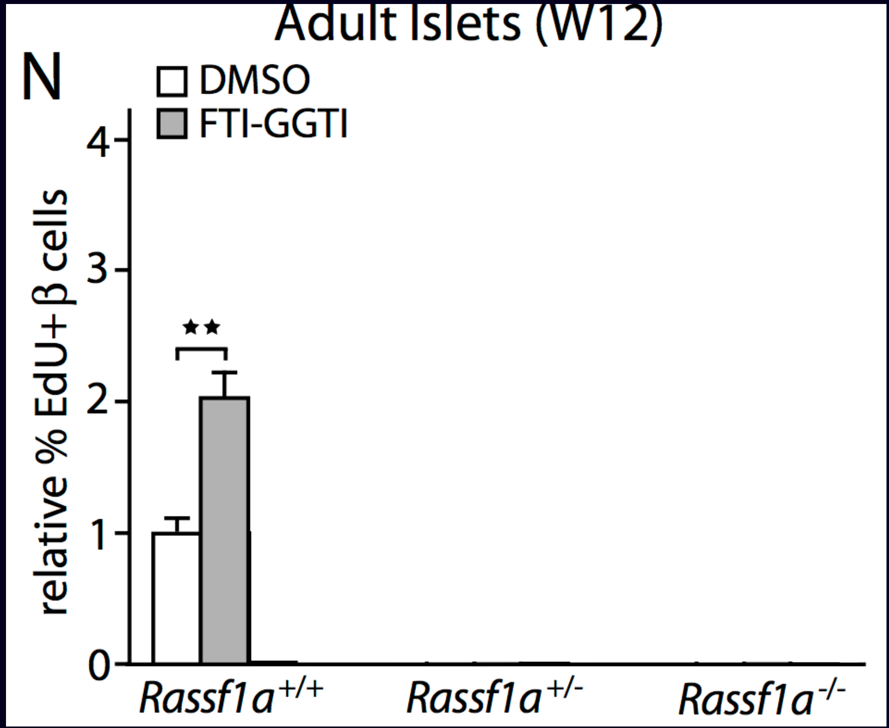
RASSF1 Inhibits Proliferation Downstream of Kras





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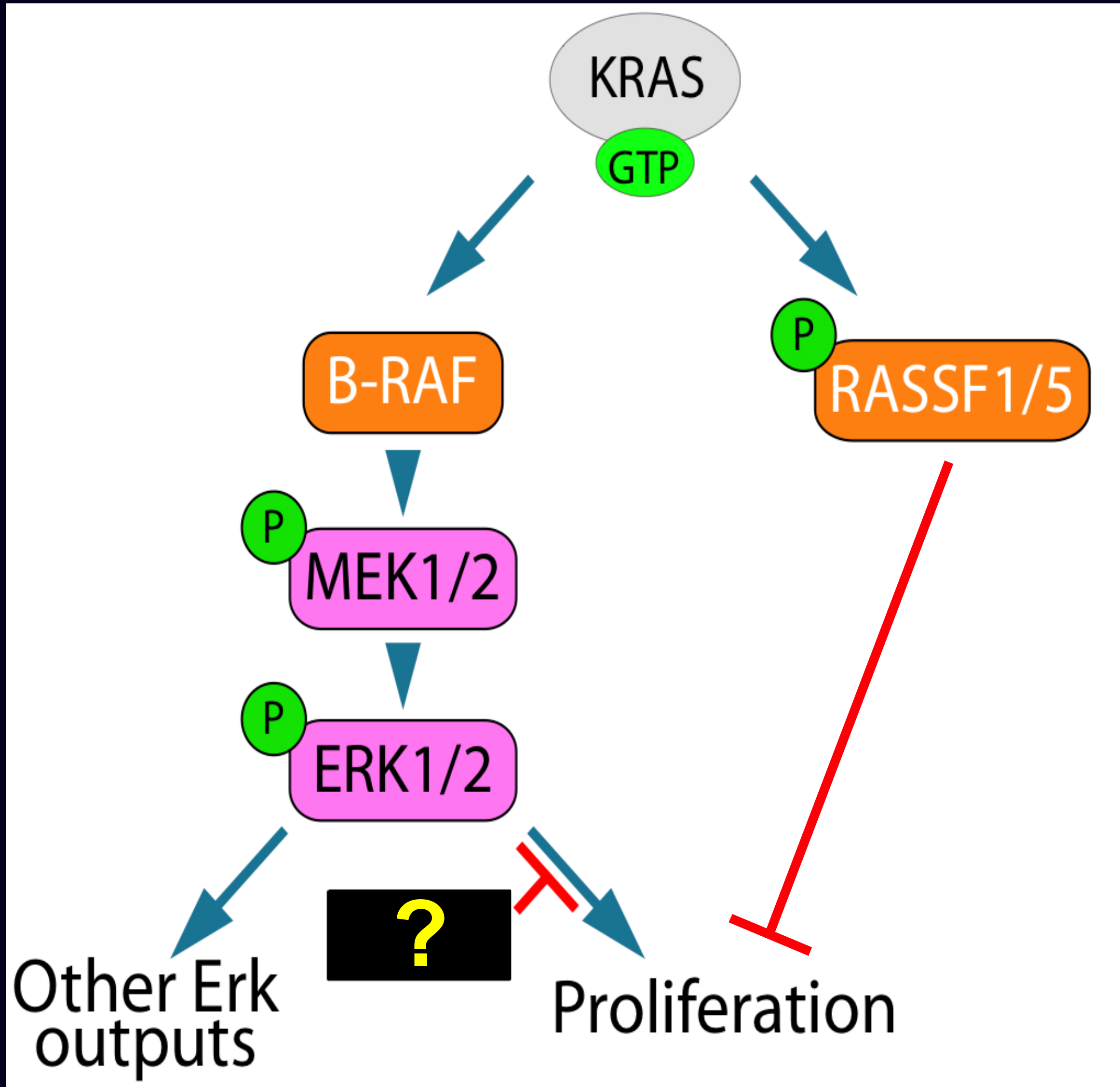
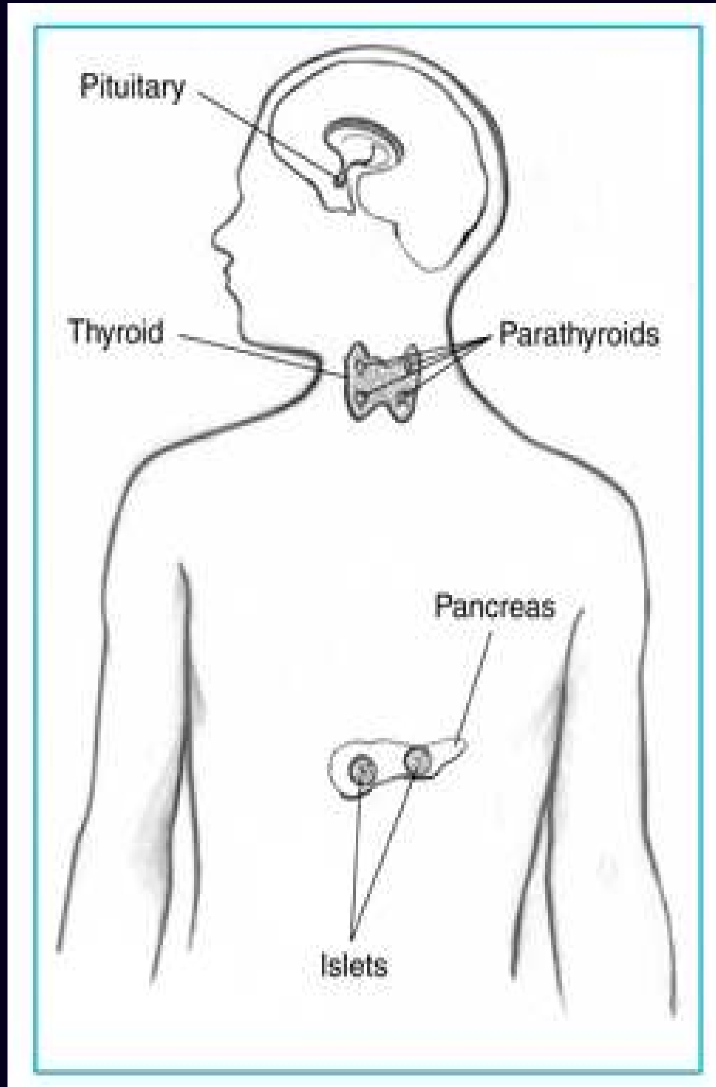
K-Ras in the β Cell

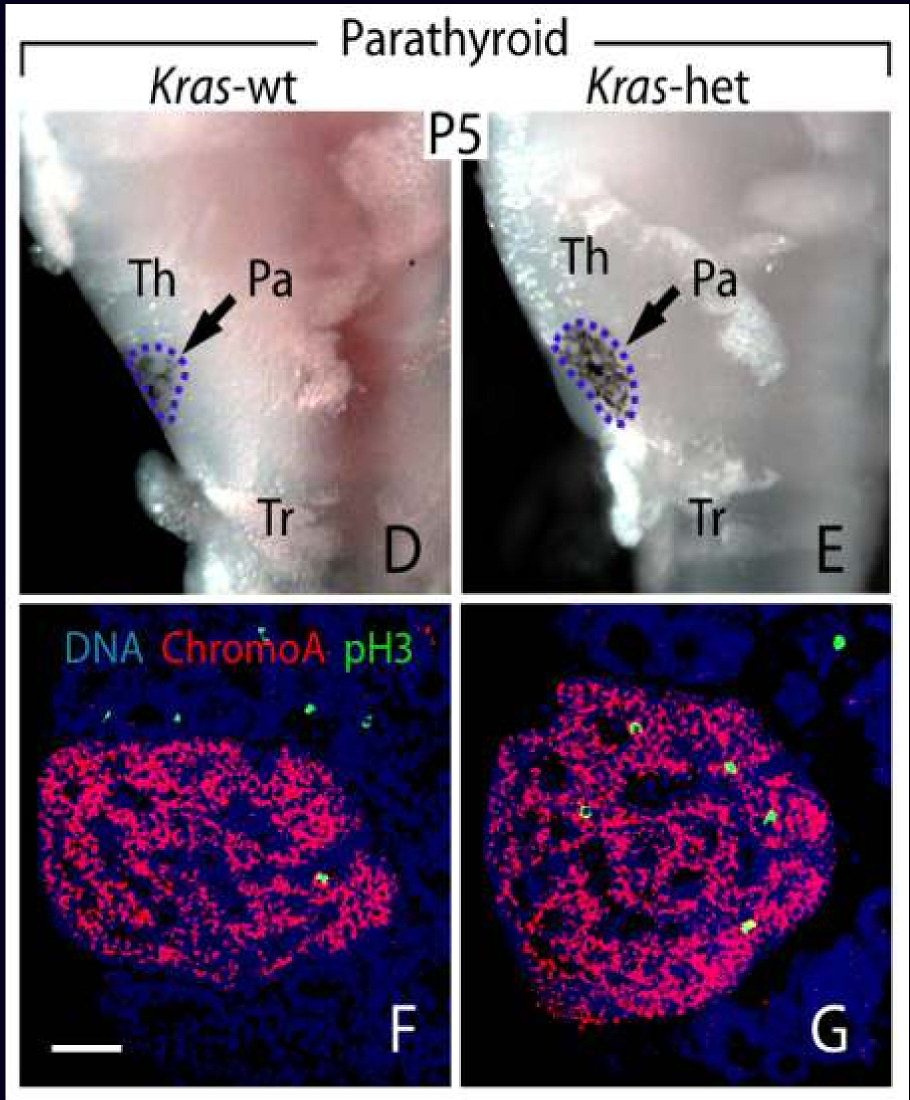


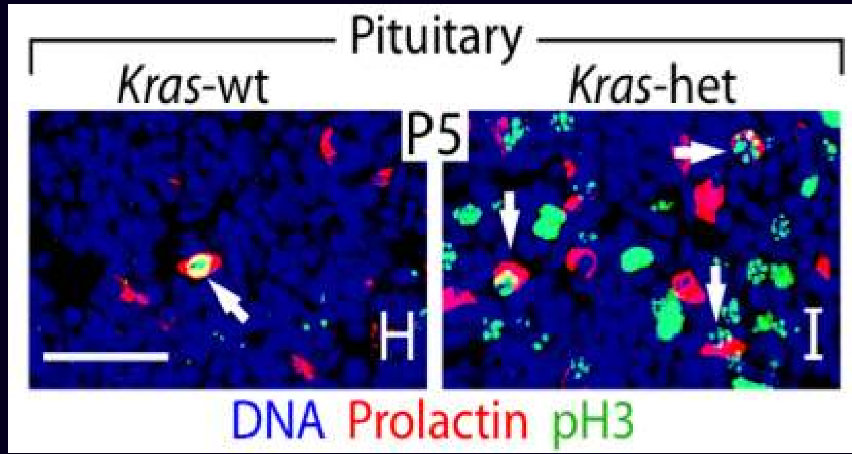
Multiple Endocrine Neoplasia Type 1

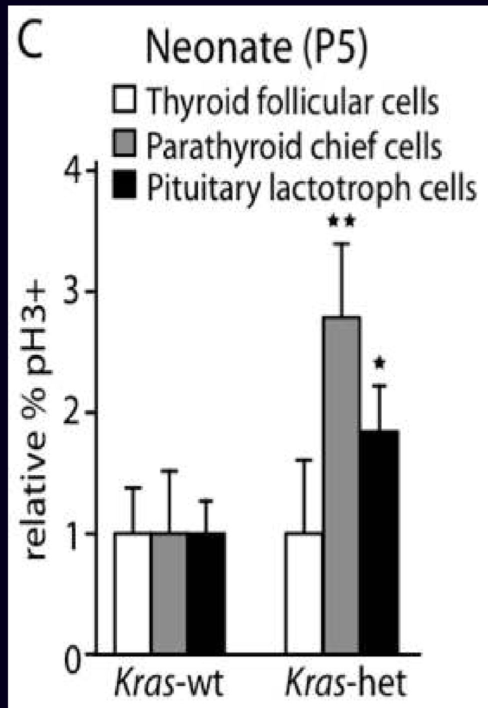
Autosomal dominant endocrine familial tumor syndrome characterized by tumors of the pancreatic islets (gastrinomas and insulinomas), parathyroids, pituitary, and adrenal cortex and less commonly other neuroendocrine tumors caused by heterozygous inactivating mutations of the *MEN1* gene, which encodes the endocrine tumor suppressor Menin.



K-Ras in Menin-Sensitive Tissues







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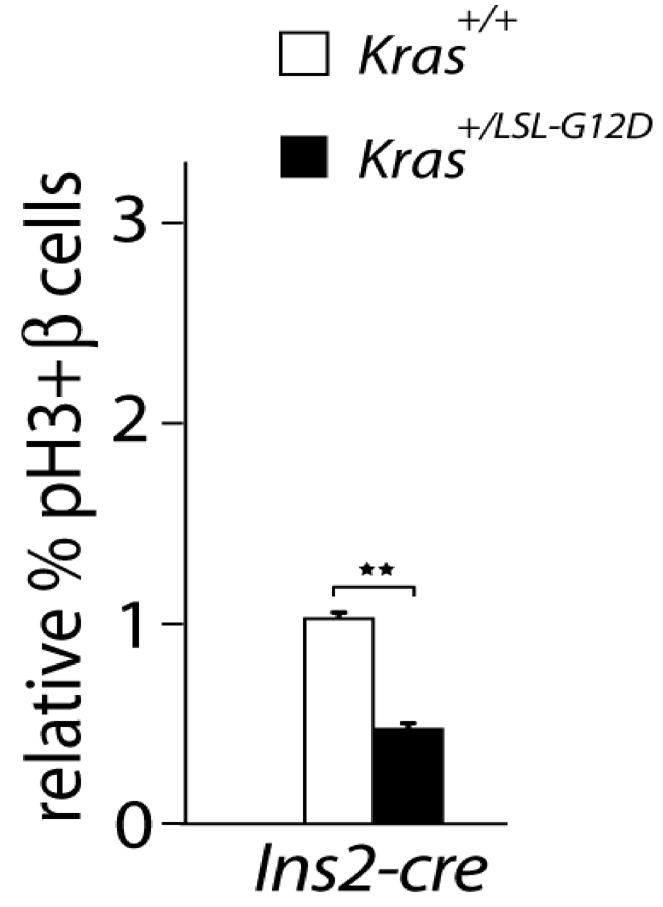
Menin Controls Kras Outputs



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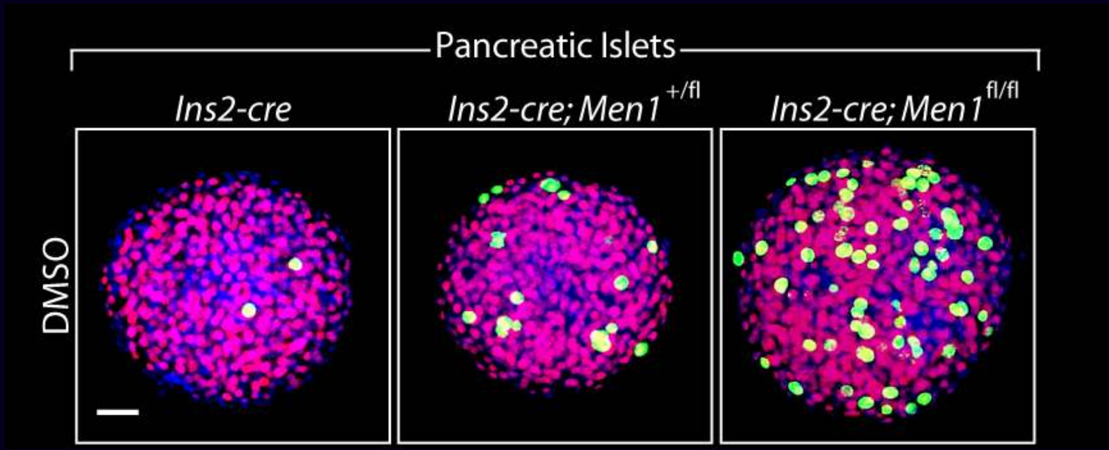
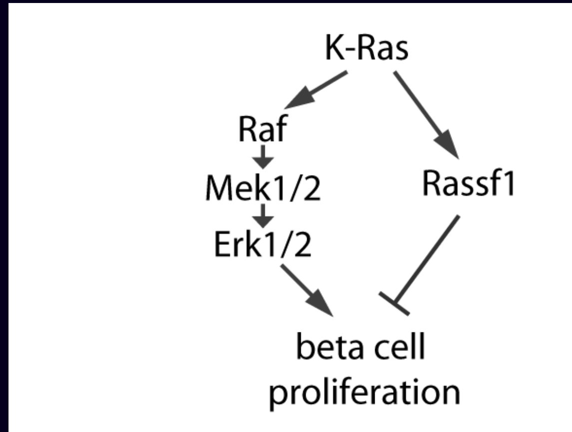
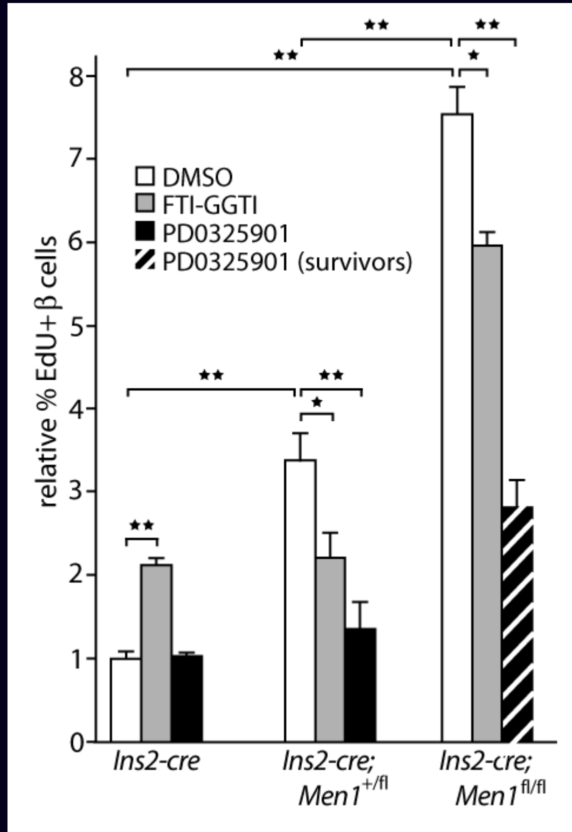
Menin Controls Kras Outputs

DNA Nkx6.1 EdU







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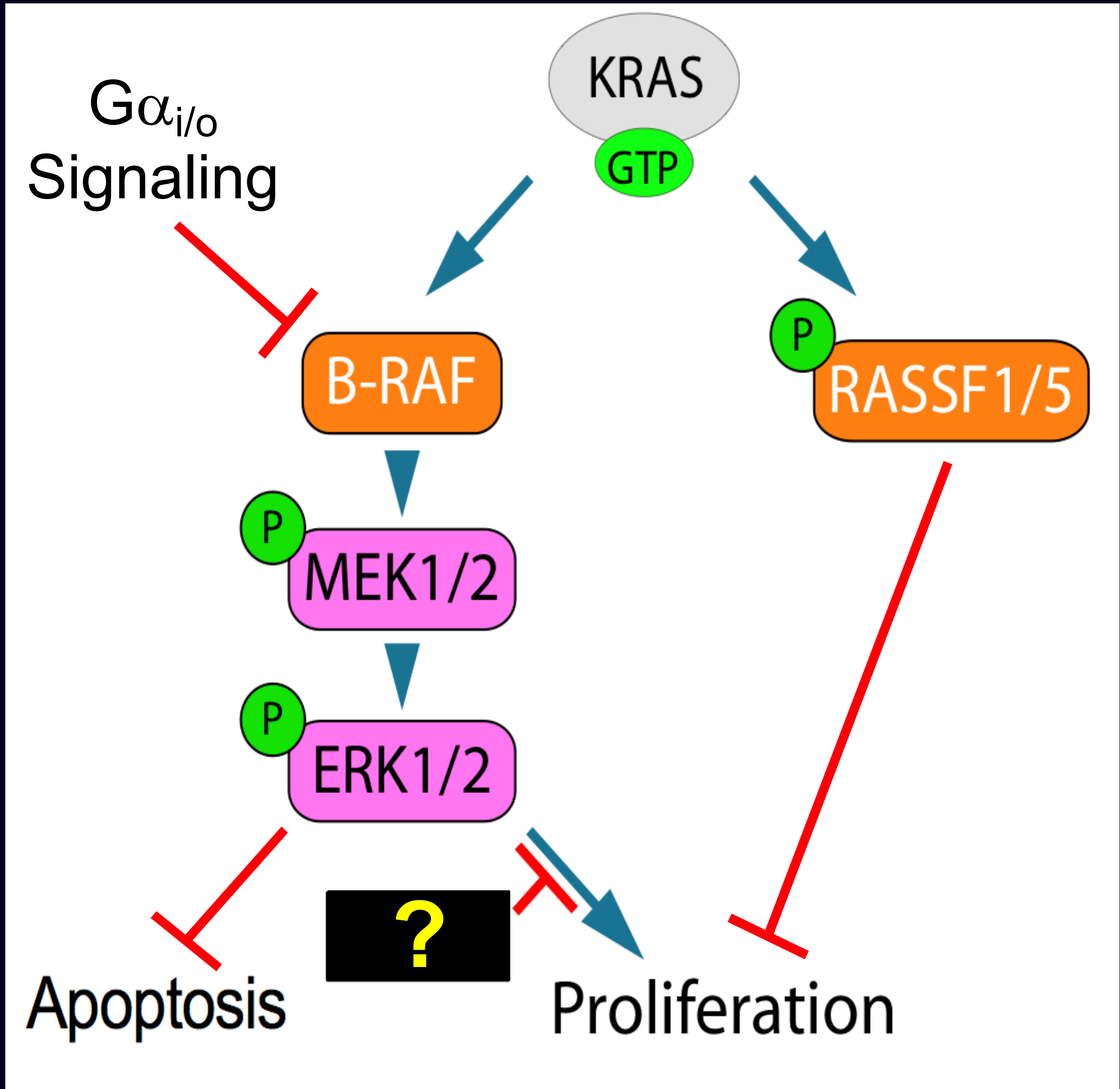
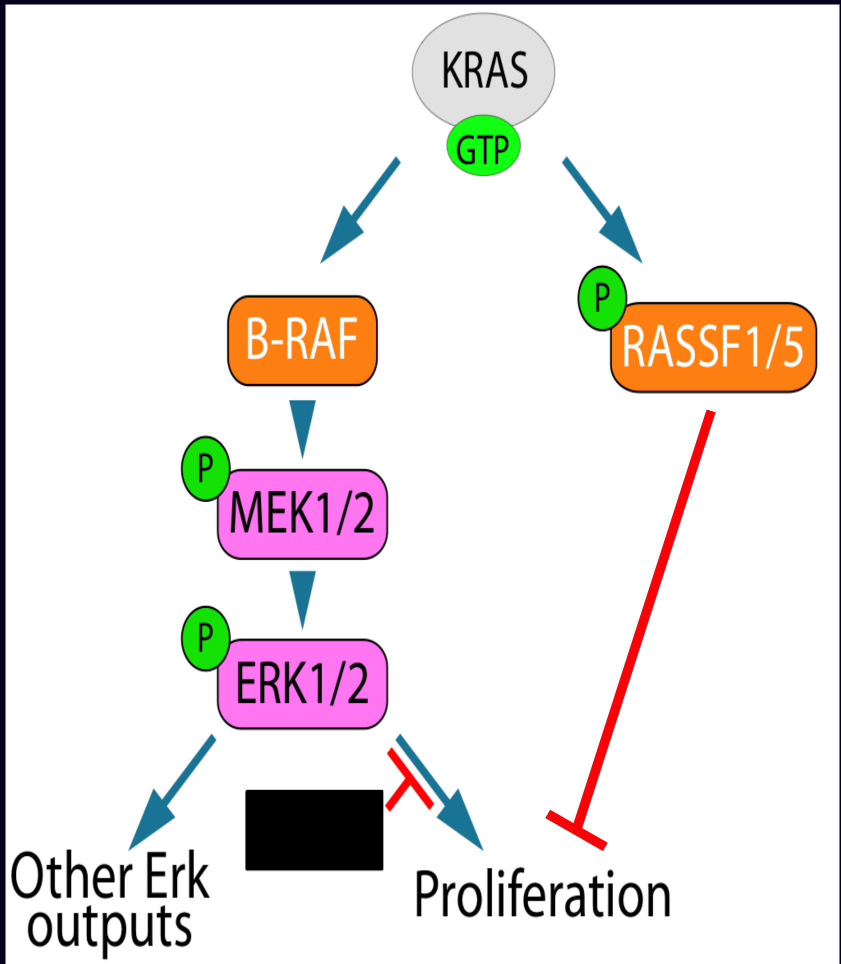
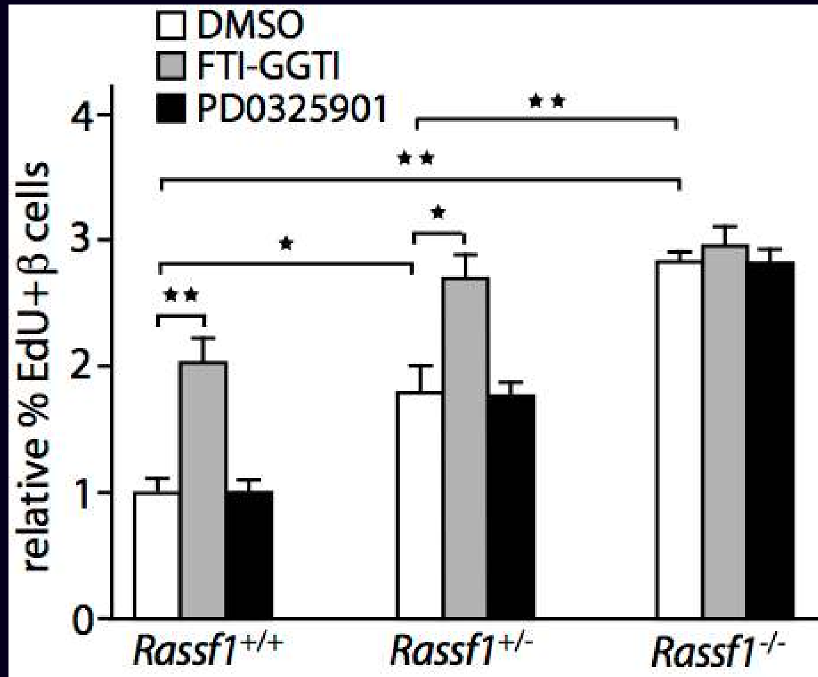
K-Ras in the β Cell



RASSF1 Inhibits Proliferation Downstream of Kras





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Summary

- During pregnancy, lactogenic hormones drive β cell serotonin production, which in turn drives β cell expansion.
- $G\alpha_{i/o}$ signals, including sympathetic signaling receptors and Htr1d, block proliferation and induce apoptosis in β cells.
- Alterations in perinatal β cell proliferation have long term effects on β cell mass.
- Kras signaling paradoxically inhibits β-cell proliferation.
- Menin acts as a gatekeeper of MAPK regulation of β-cell proliferation.
- These pathways have consequences for the role of genes, drugs, and stress in type 1 and 2 diabetes and gestational diabetes.

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