Developmental Biology of the pancreatic islet cells: a different view on islet cell expansion?

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These ideas are not new…

Pathway decision-making strategies for generating pancreatic β-cells: systems biology or hit and miss?

Jan Jensen

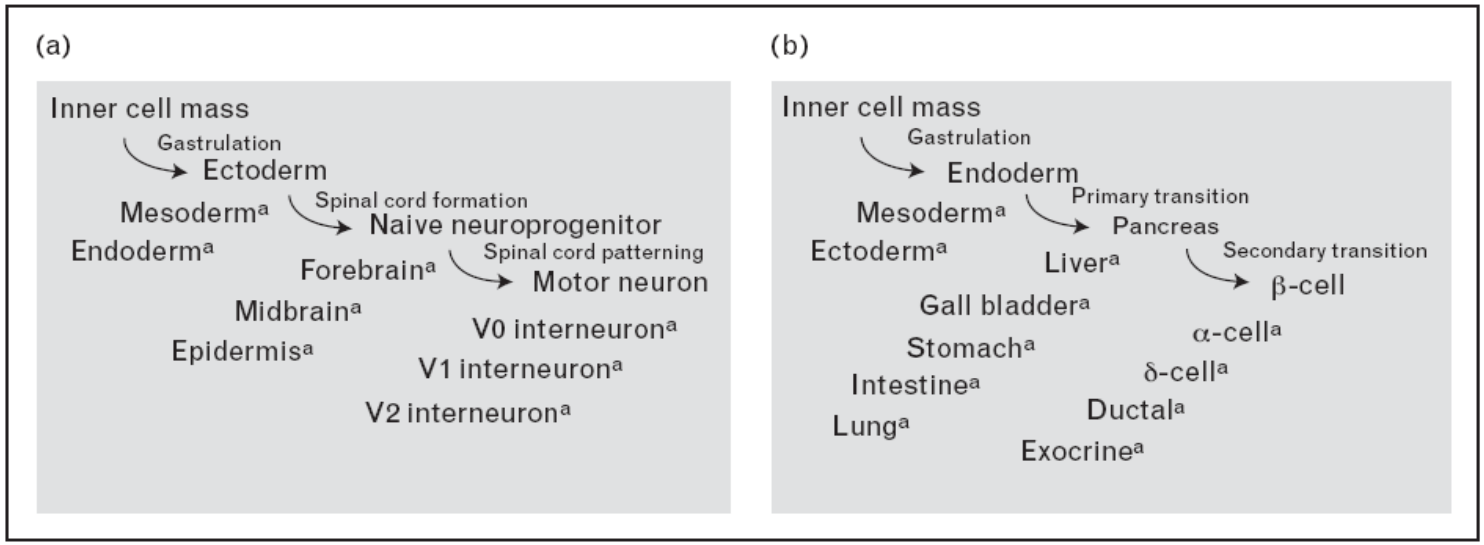
Current Opinion in Endocrinology, Diabetes & Obesity 2007, 14:277–282

subjects discussed :

- Directed Differentiation (DD) should? recapitulate normal development
- Method selection strategy
- Assay formats
- Level of bioinformatics use, need of software

Two different paths, but method identical

Figure 1 Developmental programs of motor neurons versus pancreatic β-cells



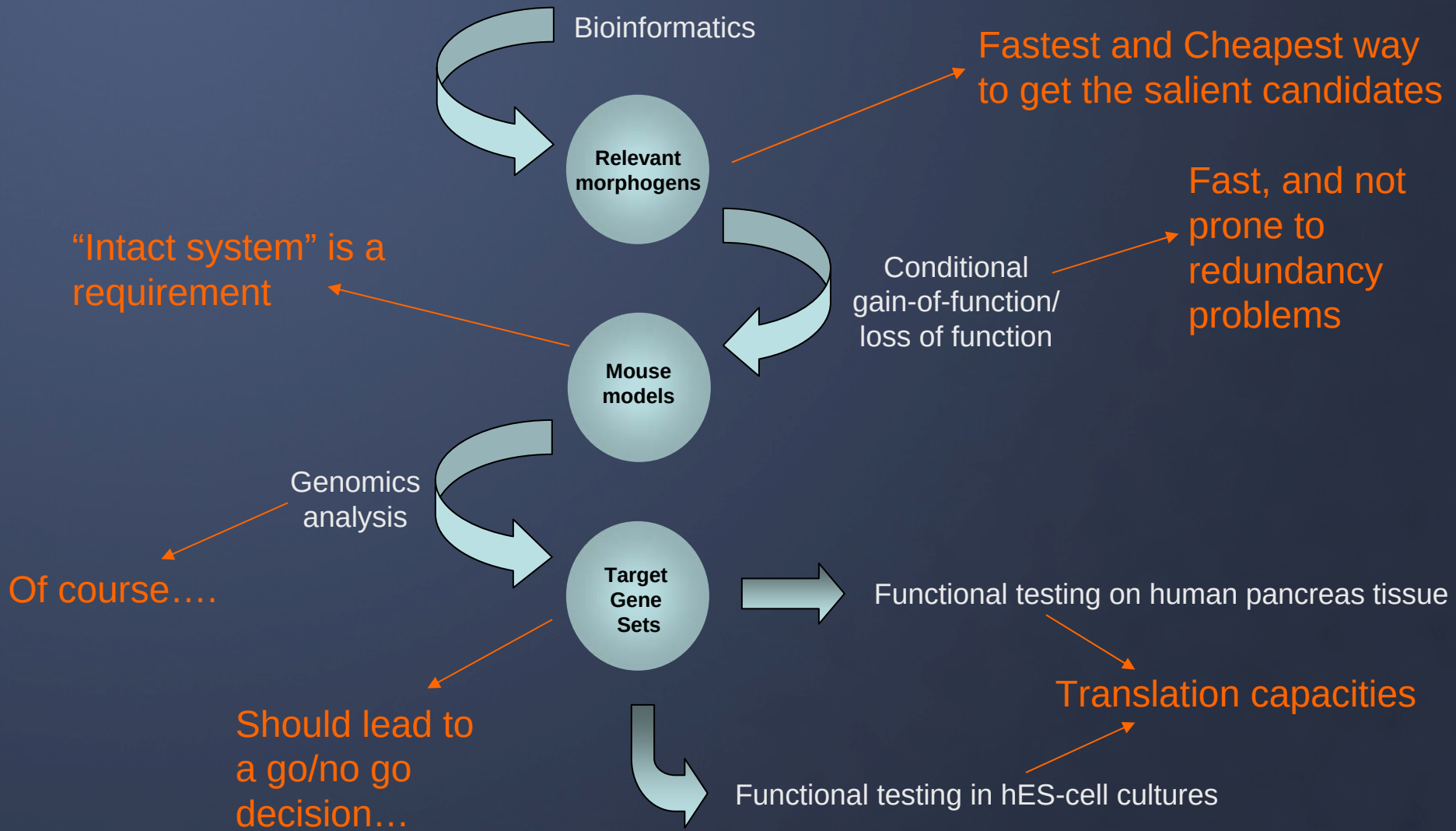
Shown are the developmental programs of (a) motor neurons and (b) pancreatic β-cells. In both cases, a progressive restriction of fates occurs, as the cells become increasingly specified. Each step is guided by signaling networks that help to promote a specific fate in favor of alternative but undesired fates. The success of a directed differentiation schema is judged by the efficiency with which such alternative fates are disallowed. [a]Alternative but undesired fates.

"Applied Developmental Biology"

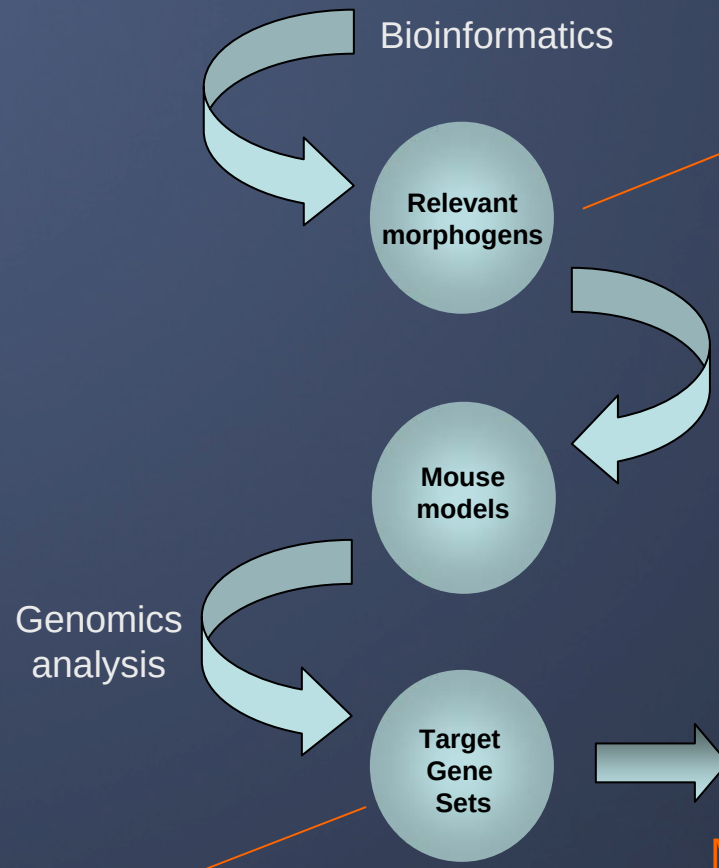
The Pancreatic Progenitor Project (P^3)

"Is a knowledge-gathering project attempting to provide information that allows project participants to successfully derive pancreatic beta-cells from either adult pancreatic cells or human ES-cells"

How to do it scientifically – and why



FGF10 – Behind the success of D'Amour et al.…



FGF10 is detected

pTRE2-FGF10; Pdx1-tTA

Functional testing on human pancreas tissue

May FGF10 play a role in adult progenitor maintenance…?

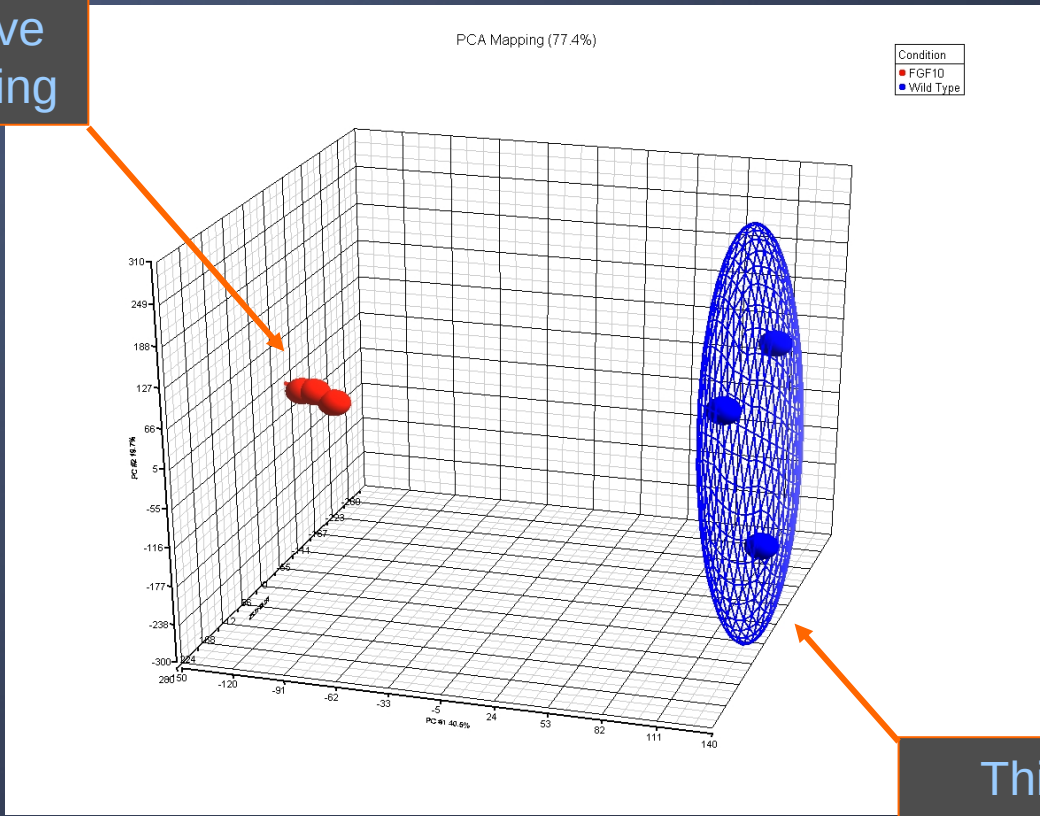
Functional testing in hES-cell cultures

FGF10 leads to progenitor maintenance.
Pdx1, Etv4 and notch activation.
Activin and Sdf1 is induced but not Wnt, or BMP components
Leads to a distalization/exocrine patterning.

Use FGF10 to reinforce the pancreatic state, but! - be careful when applying

Genomics analysis of conditional FGF10 pancreas

This is the pancreatic progenitor cell state, hyperactive in FGF10 signaling



This is normal E16.5 pancreas

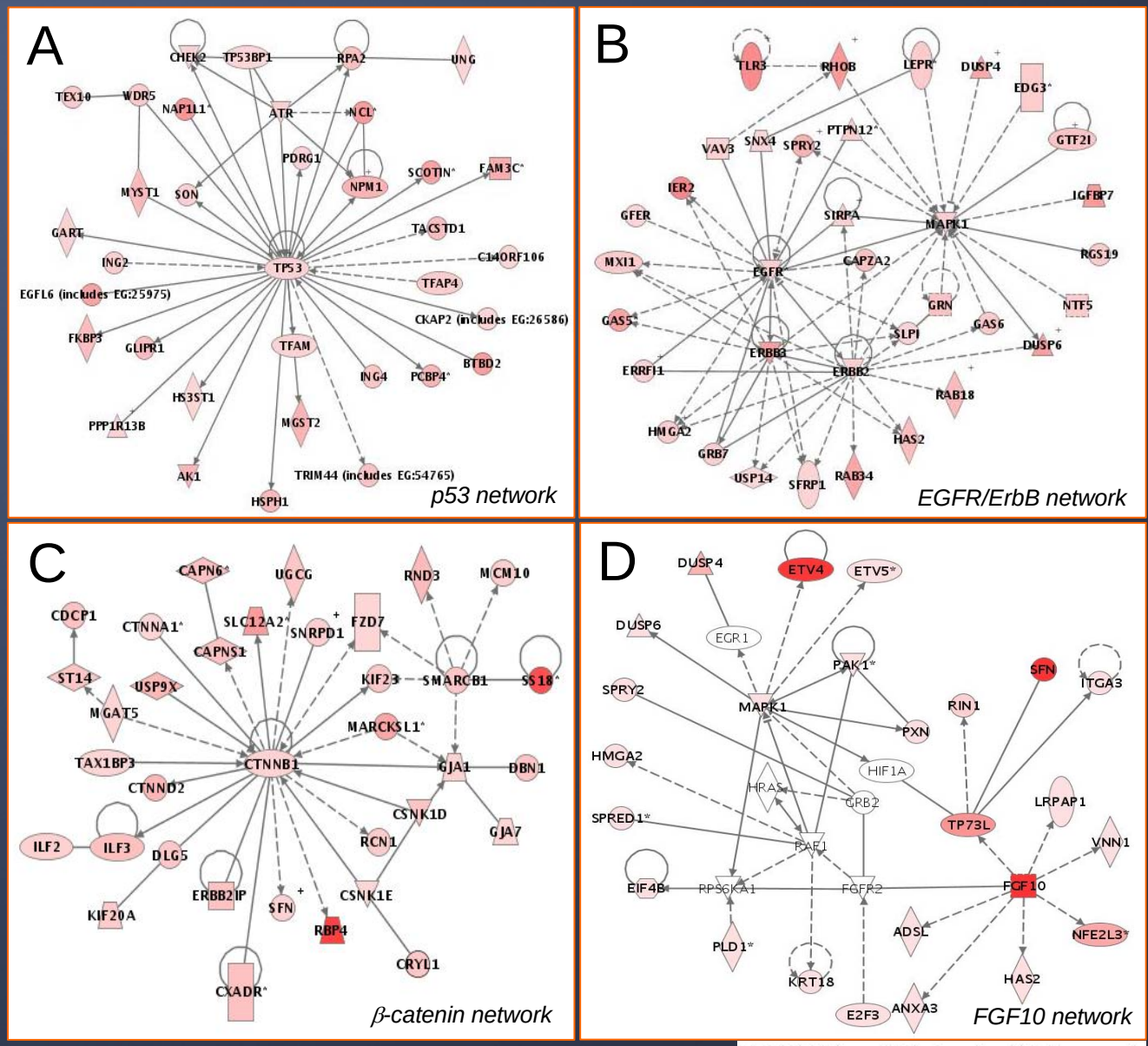
Genomics analysis of conditional FGF10 pancreas

Exocrine-specific genes							
probeset ID	P-value	T-value	Mean, DTG	Mean, WT	DTG/WT	Gene Name	*symbol*
1435012_x_at	2.8E-04	-12.0	36288.6	91394.9	0.397	elastase 3	*Ela3*
1433573_x_at	2.5E-03	-6.8	42757.1	87565.3	0.488	protease, serine, 2	*Prss2*
1416055_at	3.5E-04	-11.3	47014.5	86992.4	0.540	amylase 2, pancreatic	*Amy2*
1448281_a_at	8.1E-04	-9.1	22597.4	85907.0	0.263	elastase 2A	*Ela2a*
1416523_at	4.8E-04	-10.4	10321.6	85440.2	0.121	ribonuclease, RNase A family, 1	*Rnase1*
1415805_at	2.0E-03	-7.2	37996.4	83353.0	0.456	colipase, pancreatic	*Clps*
1417257_at	1.9E-03	-7.3	33000.2	82339.6	0.401	carboxyl ester lipase	*Cel*
1423693_at	1.2E-04	-14.7	14576.4	74443.2	0.196	elastase 1, pancreatic	*Ela1*
1428062_at	2.1E-03	-7.1	37527.6	74170.6	0.506	carboxypeptidase A1	*Cpa1*
1448220_at	5.0E-03	-5.6	37354.2	70708.6	0.528	chymotrypsinogen B1	*Ctrb1*
1438612_a_at	1.4E-03	-8.0	31656.1	70477.6	0.449	colipase, pancreatic	*Clps*
1454623_at	1.2E-03	-8.3	30911.6	69402.5	0.445	carboxypeptidase A2, pancreatic	*Cpa2*
1415777_at	2.4E-03	-6.8	34145.3	68615.1	0.498	pancreatic lipase related protein 1	*Pnliprp1*
1428102_at	4.4E-04	-10.6	9481.1	68606.1	0.138	carboxypeptidase B1	*Cpb1*
1415954_at	1.6E-05	-24.9	20472.0	63646.0	0.322	trypsin 4	*Try4*
1422682_s_at	1.0E-04	-15.4	10080.2	62619.4	0.161	trypsin 1	*Prss1*
1431763_a_at	4.7E-04	-10.5	525.7	55524.7	0.009	chymotrypsin-like	*Ctrl*
1449233_at	8.9E-05	-16.0	1963.0	8490.2	0.231	MIST1	*Bhlhb8*
1419424_at	3.3E-04	-11.4	4710.0	8919.5	0.528	pancreas specific transcription factor, 1a	*Ptf1a*
1421956_at	4.2E-05	-19.3	742.7	3944.0	0.188	rbp suppressor of hairless-like	*Rbpsuhl*
1421195_at	8.6E-06	-28.8	4286.1	26135.7	0.164	cholecystokinin A receptor	*Cckar*

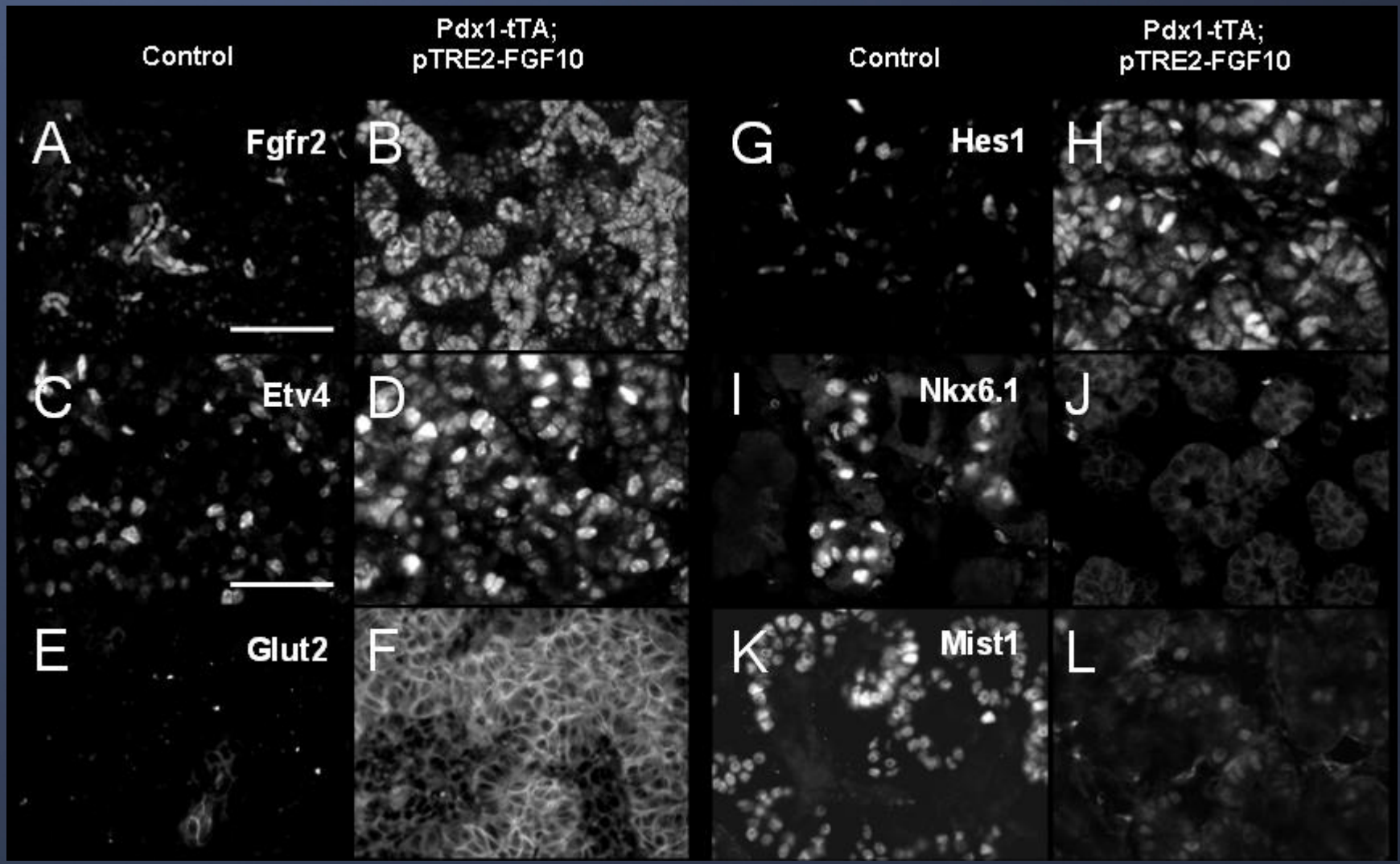
Genomics analysis of conditional FGF10 pancreas

Endocrine-specific genes							
1422446_x_at	2.9E-07	-67.6	83.8	52948.4	0.002	insulin II	*Ins2*
1422447_at	5.4E-06	-32.4	203.4	49168.8	0.004	insulin I	*Ins1*
1425952_a_at	5.2E-04	-10.2	1449.6	37850.6	0.038	glucagon	*Gcg*
1417954_at	1.9E-03	-7.3	82.6	6446.9	0.013	somatostatin	*Sst*
1448980_at	1.3E-03	-8.1	36.7	925.7	0.040	ghrelin	*Ghrl*
1423510_at	5.1E-03	-5.6	66.2	20749.5	0.003	islet amyloid polypeptide	*Iapp*
1418149_at	4.4E-03	-5.8	259.8	2188.2	0.119	chromogranin A	*Chga*
1448628_at	1.3E-03	-8.0	57.3	2498.3	0.023	secretogranin III	*Scg3*
1424009_at	3.2E-03	-6.3	252.6	2837.3	0.089	regenerating islet-derived 3 delta	*Reg3d*
1450708_at	2.6E-02	-3.5	350.1	2819.1	0.124	secretogranin II	*Scg2*
1423150_at	1.6E-03	-7.6	201.4	1514.5	0.133	secretogranin V	*Scg5*
1448312_at	3.7E-04	-11.1	48.3	1932.3	0.025	proprotein convertase 2	*Pcsk2*
1421396_at	4.7E-05	-18.8	32.3	1049.5	0.031	proprotein convertase 1	*Pcsk1*
1423529_at	2.8E-02	-3.4	11.3	1574.3	0.007	glucose-6-phosphatase, catalytic, 2	*G6pc2*
1422312_a_at	3.3E-03	-6.3	7.7	414.4	0.019	neurogenin 3	*Neurog3*
1452526_a_at	7.6E-04	-9.3	5.4	250.8	0.021	paired box gene 6	*Pax6*
1426412_at	1.2E-03	-8.3	17.3	781.3	0.022	neurogenic differentiation 1	*Neurod1*
1450042_at	2.0E-03	-7.1	10.6	175.9	0.060	aristaless related homeobox gene	*Arx*
1426298_at	2.8E-04	-12.0	20.4	169.0	0.121	Iroquois related homeobox 2	*Irx2*
1421399_at	2.8E-04	-12.0	54.0	436.4	0.124	insulinoma-associated 1	*Insm1*
1451716_at	1.7E-03	-7.5	70.8	556.4	0.127	v-maf protein B	*Mafb*
1422773_at	2.6E-04	-12.2	27.6	193.7	0.143	myelin transcription factor 1	*Myt1*
1451983_at	1.1E-02	-4.5	51.1	322.3	0.159	Iroquois related homeobox 1	*Irx1*
1450723_at	1.3E-04	-14.6	266.7	1247.5	0.214	ISL1	*Isl1*
Ductal specific genes							
1449199_at	5.5E-03	-5.5	2880.2	4012.6	0.718	mucin 1	*Muc1*
1417828_at	8.3E-06	-29.1	673.2	7835.4	0.086	aquaporin 8	*Aqp8*
1416203_at	2.3E-03	-6.9	792.6	1886.1	0.420	aquaporin 1	*Aqp1*
1434464_at	5.5E-04	-10.1	575.4	12895.9	0.045	aquaporin 12	*Aqp12*

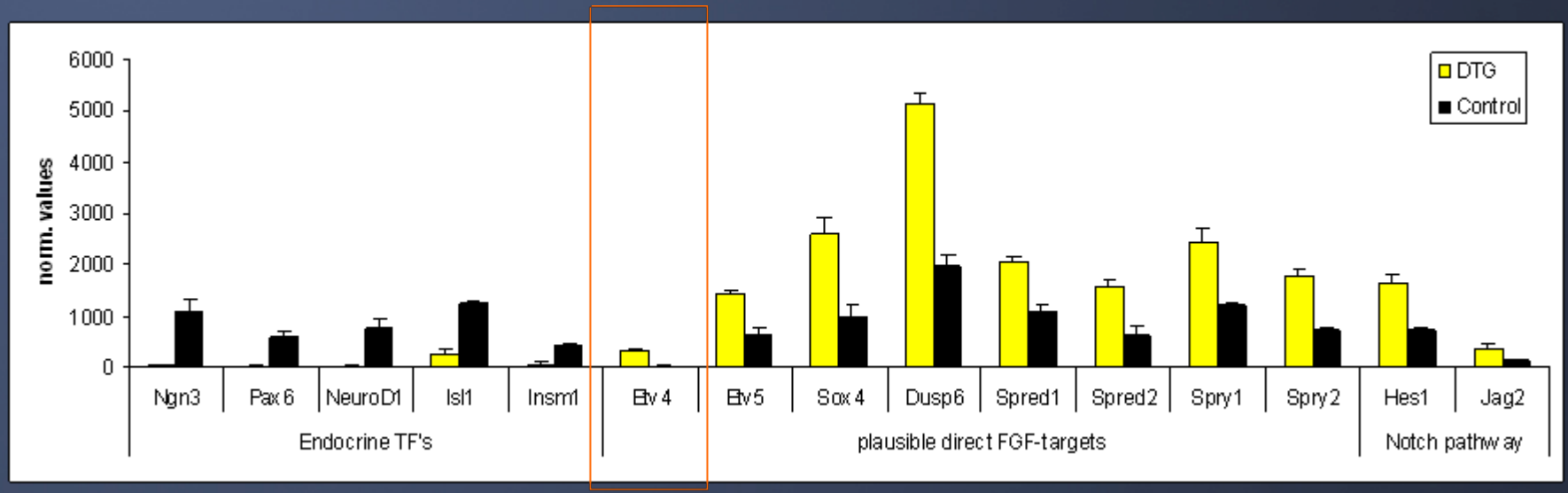
Genomics analysis of conditional FGF10 pancreas

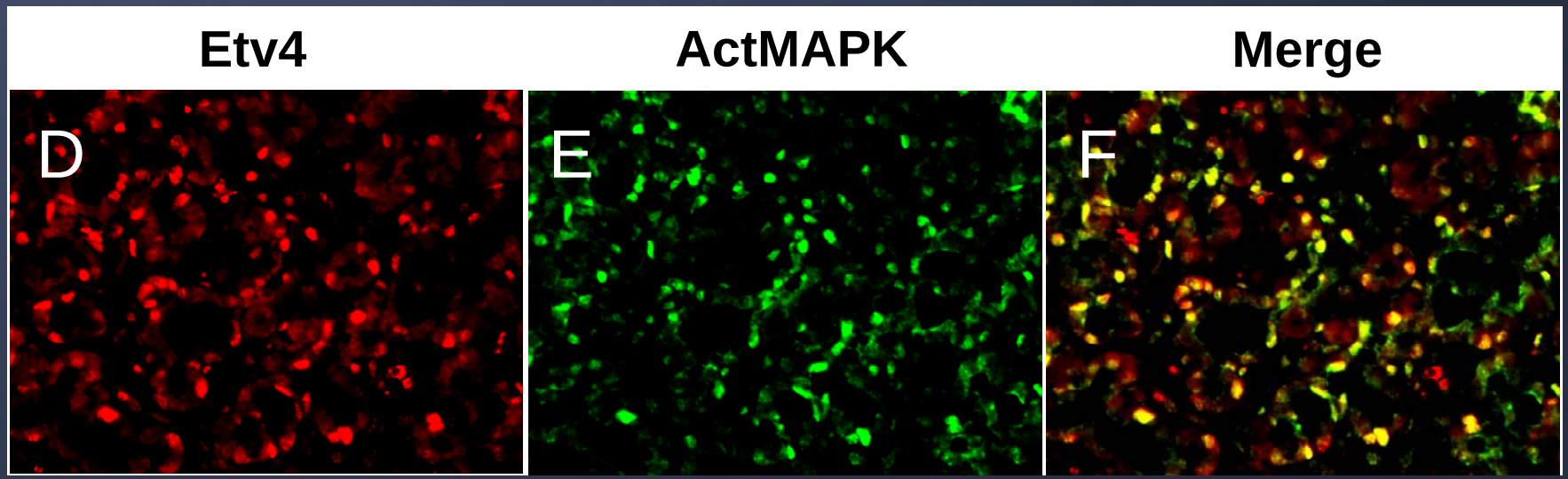


Phenotype of FGF10-arrested progenitors (E16.5)

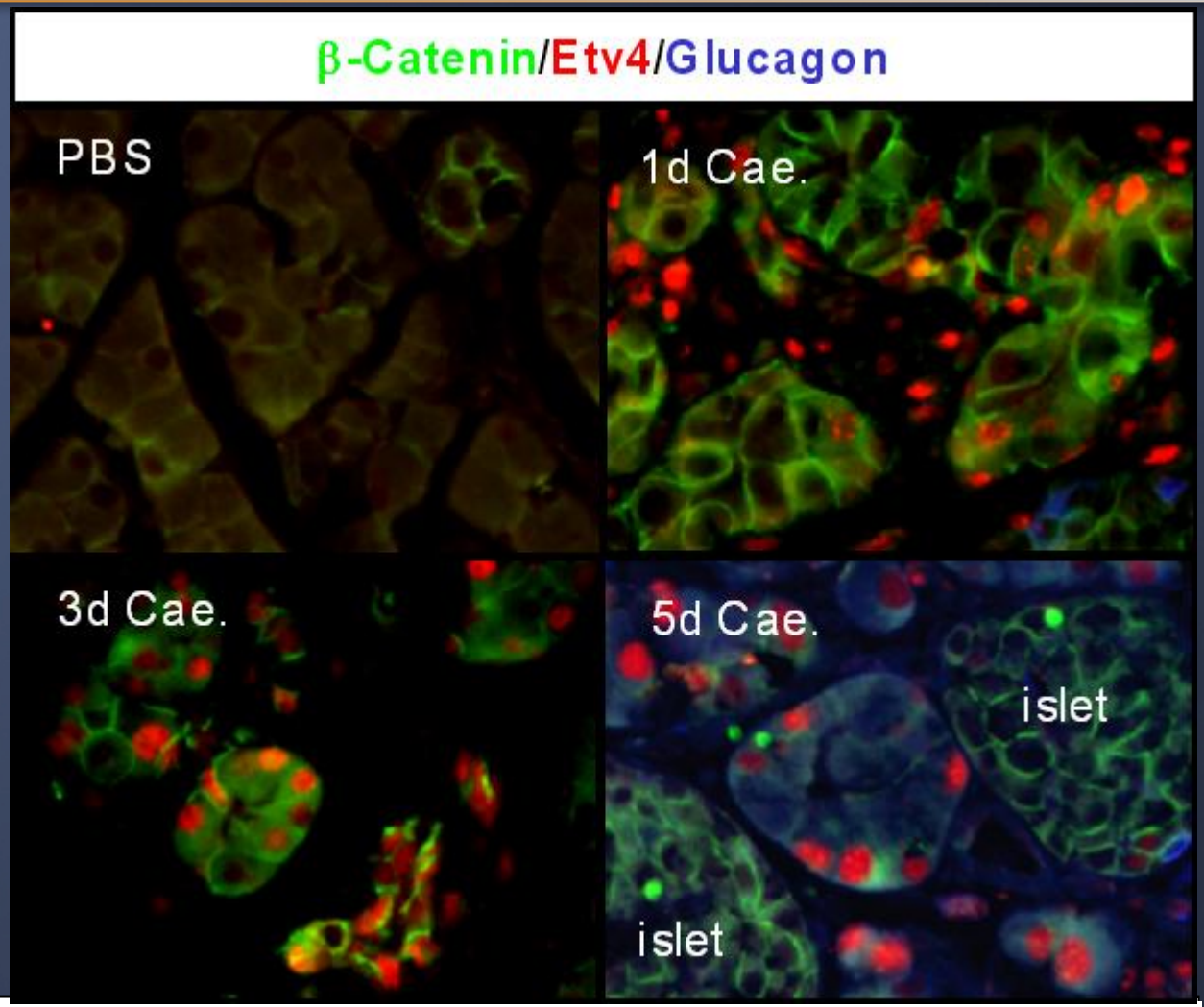


Etv4 is a plausible FGF10-target gene in pancreas





Etv4 is re-expressed during pancreatic regeneration



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Recapitulation of Elements of Embryonic Development in Adult Mouse Pancreatic Regeneration

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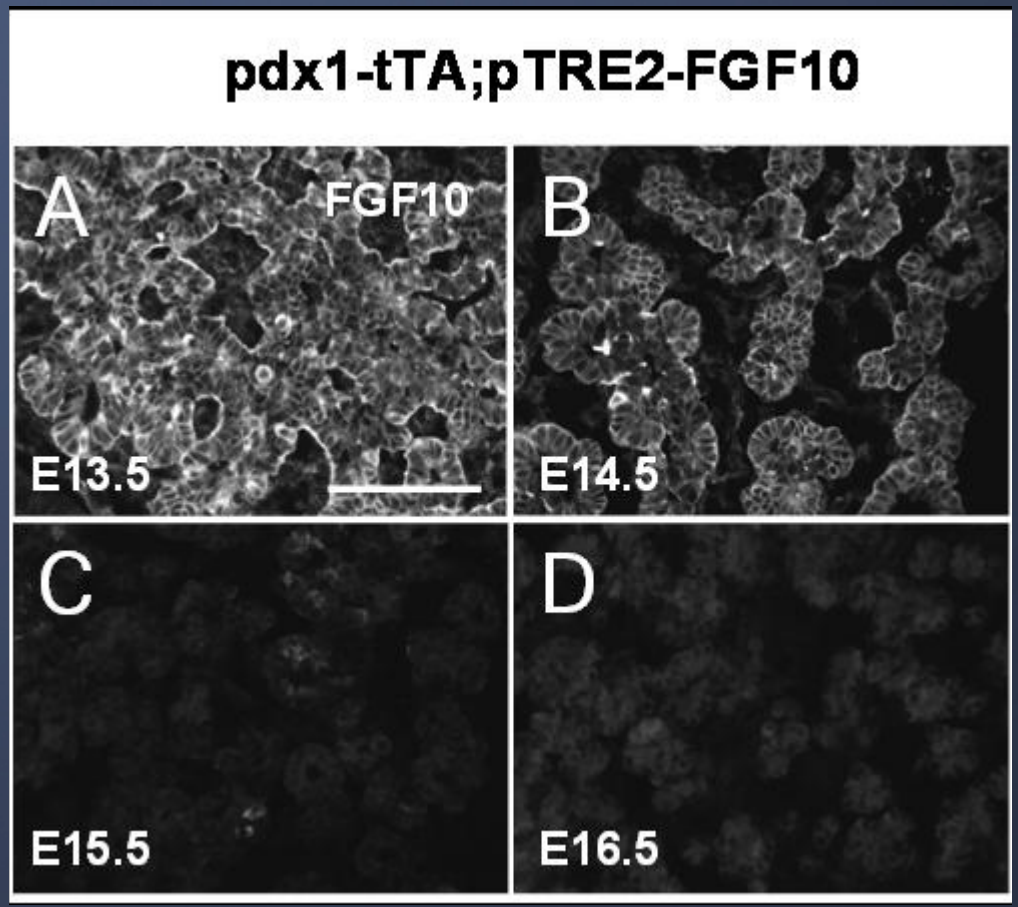
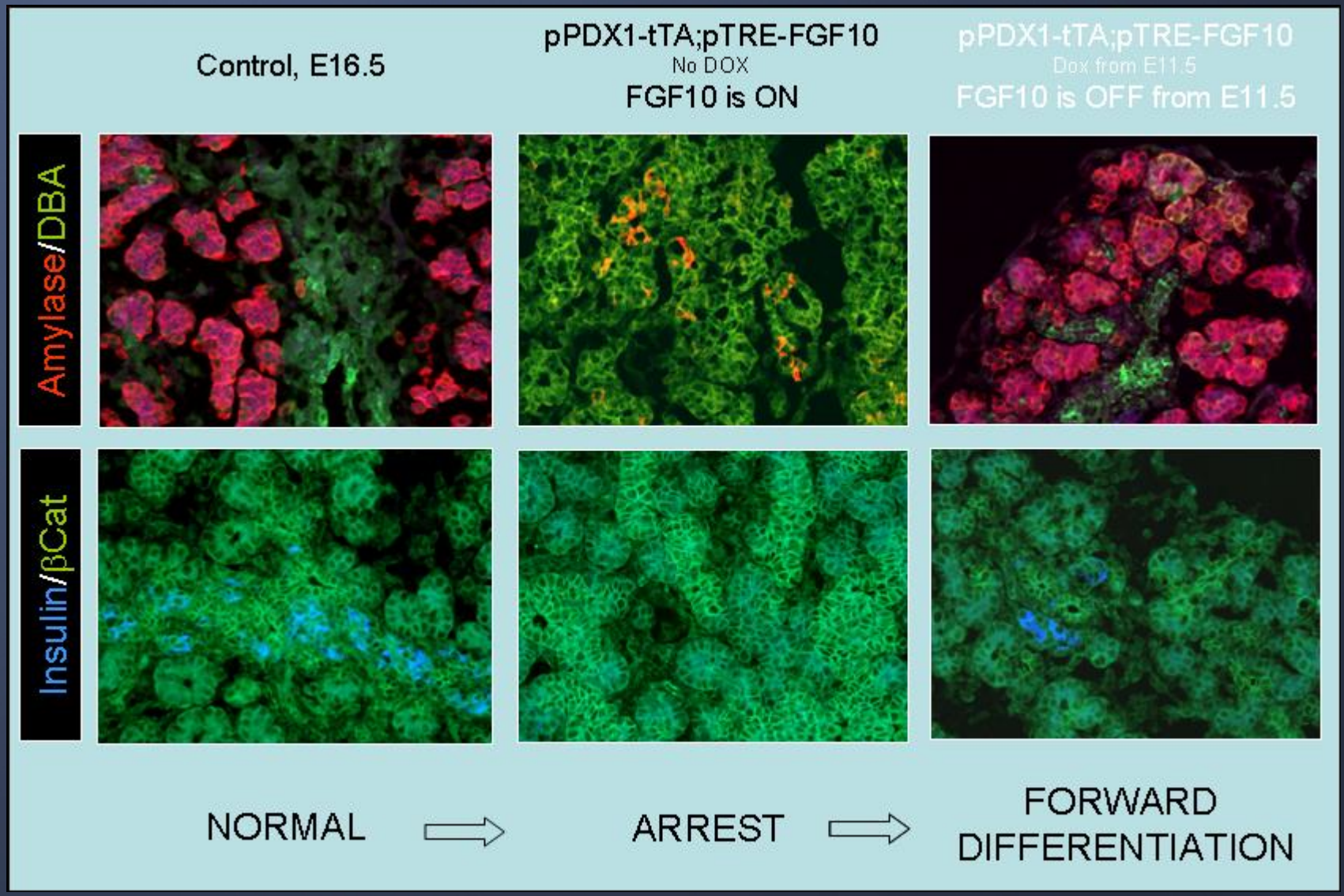
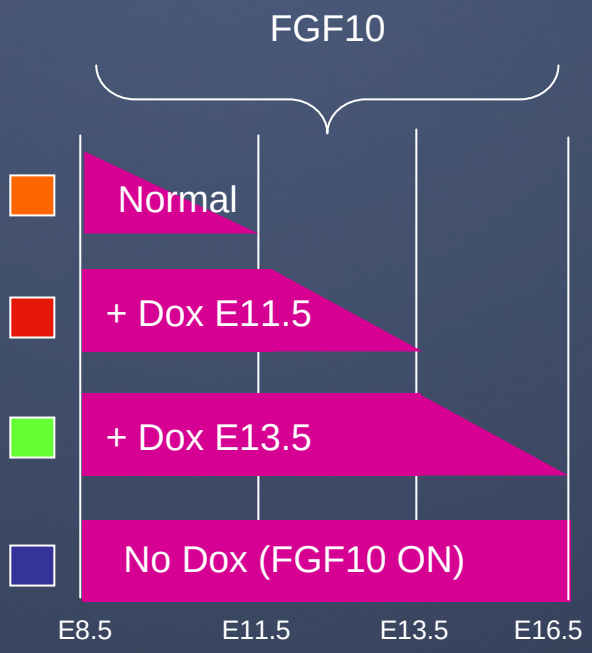
Attenuation of transgenic FGF10 expression



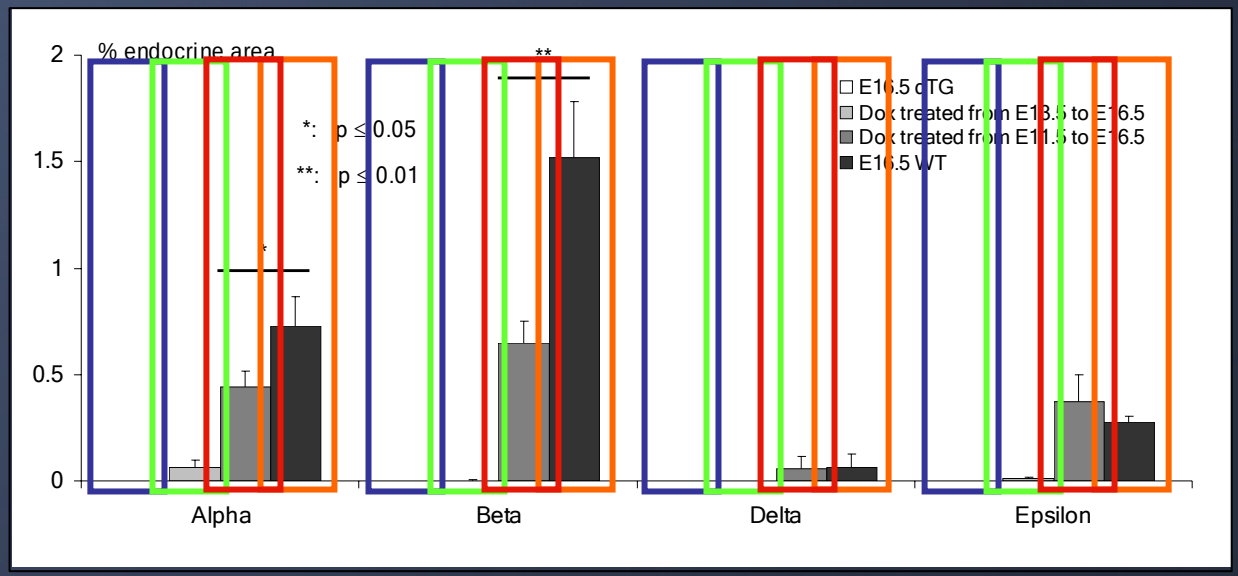
FGF10 mediates *reversible* pancreatic progenitor arrest



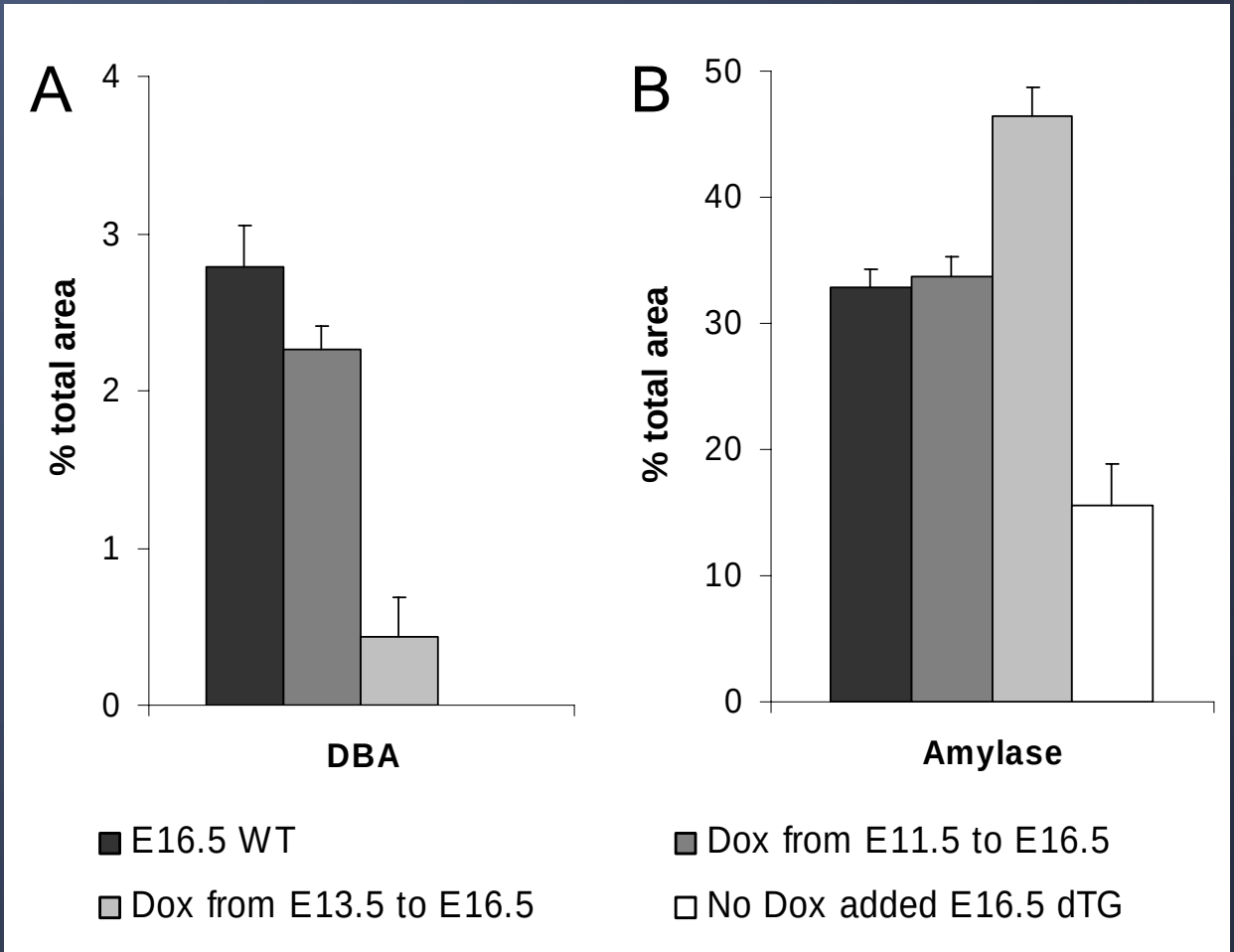
The window of endocrine competence is limited in time



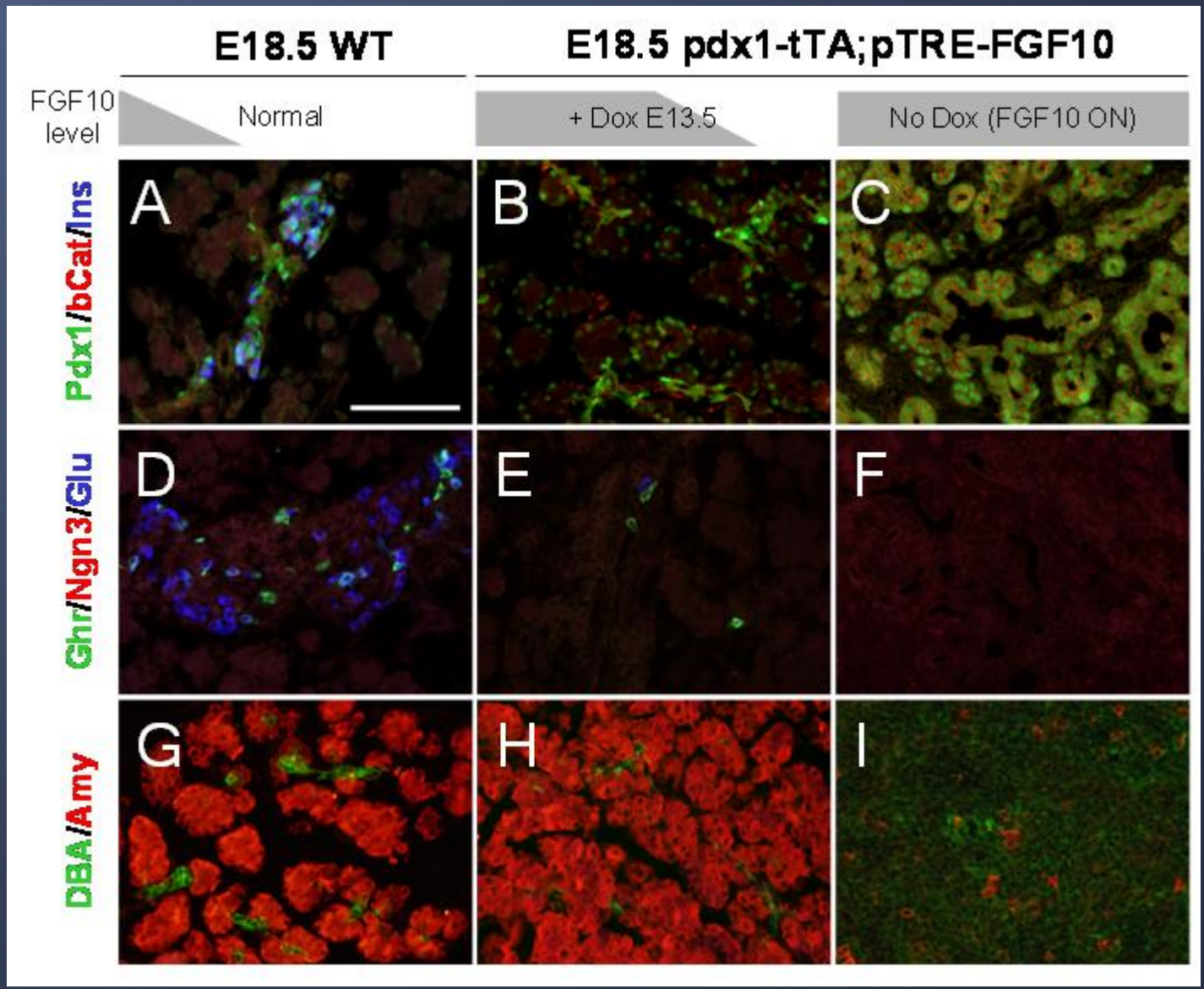
pTRE2-FGF10;Pdx1-tTA



Temporally restricted ductal development



Time past FGF10 attenuation does not lead to endocrine competence recovery



Simplified model of a temporal competence window