Analysis of the plasticity of duct cells in the embryonic and adult pancreas

Myriam Solar
Hospital Clinic de Barcelona
Barcelona 2009

Major periods of formation of new β-cells:

1- Embryogenesis (*secondary transition*)

2- Postnatal life

Neonatal period

Long-term growth

Regeneration in response to injury

Hnf1β is a specific marker for primitive and adult pancreatic duct epithelium

***Hnf6* and *Tcf2* (MODY5) are linked in a gene network operating in a precursor cell domain of the embryonic pancreas**

Miguel A. Maestro[1], Sylvia F. Boj[1], Reini F. Luco[1], Christophe E. Pierreux[3], Judit Cabedo[1], Joan M. Servitja[1], Michael S. German[2], Guy G. Rousseau[3], Frédéric P. Lemaigre[3] and Jorge Ferrer[1,*]

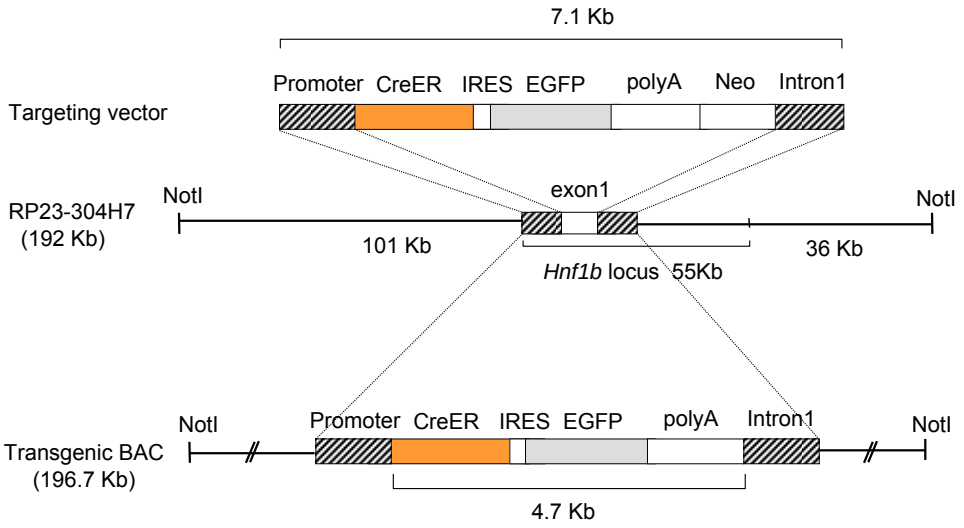
Expression of HNF-4α (MODY1), HNF-1β (MODY5), and HNF-1α (MODY3) proteins in the developing mouse pancreas

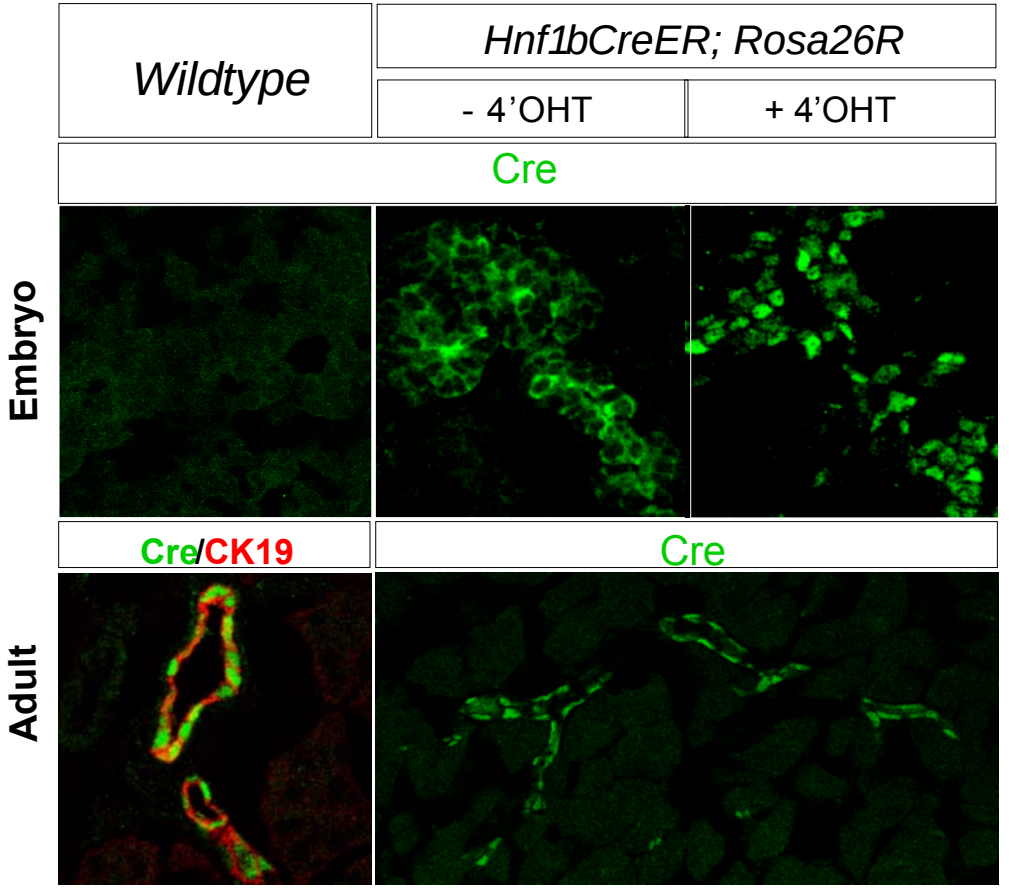
Takao Nammo [a], Kazuya Yamagata [a,*], Toshiya Tanaka [b], Tatsuhiko Kodama [b], Frances M. Sladek [c], Kenji Fukui [a], Fumie Katsube [a], Yoshifumi Sato [a], Jun-ichiro Miyagawa [a], Iichiro Shimomura [a]

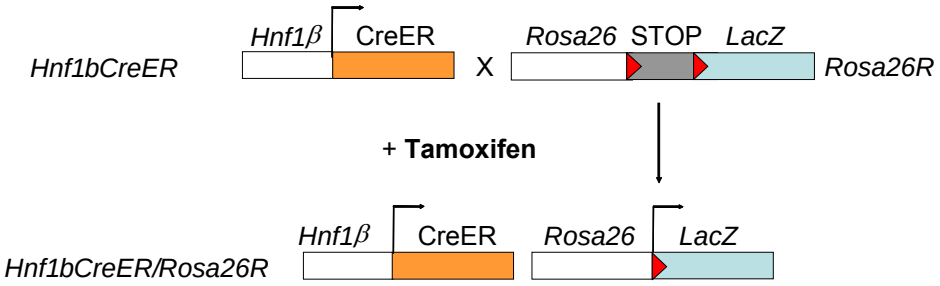
Snail2, a mediator of epithelial-mesenchymal transitions, expressed in progenitor cells of the developing endocrine pancreas

J. Michael Rukstalis, Joel F. Habener *

Generation of a BAC transgenic to trace the lineage of pancreatic ducts

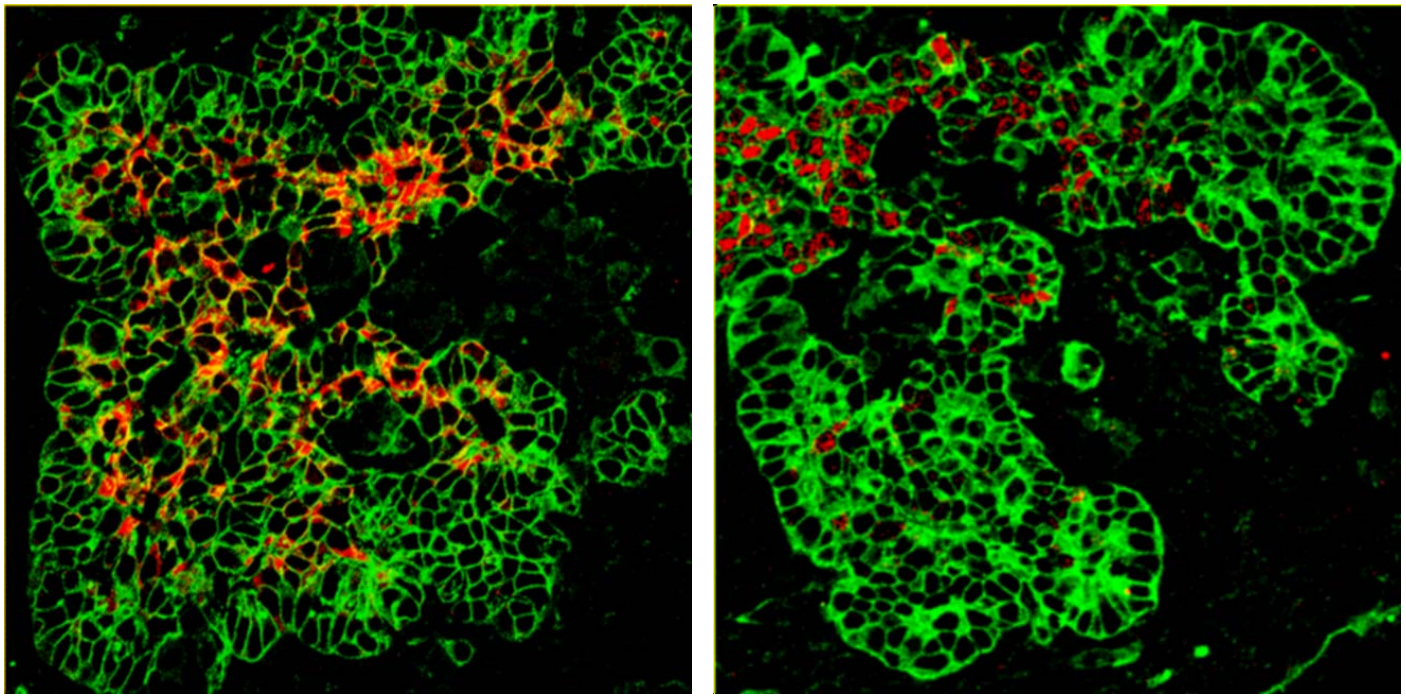




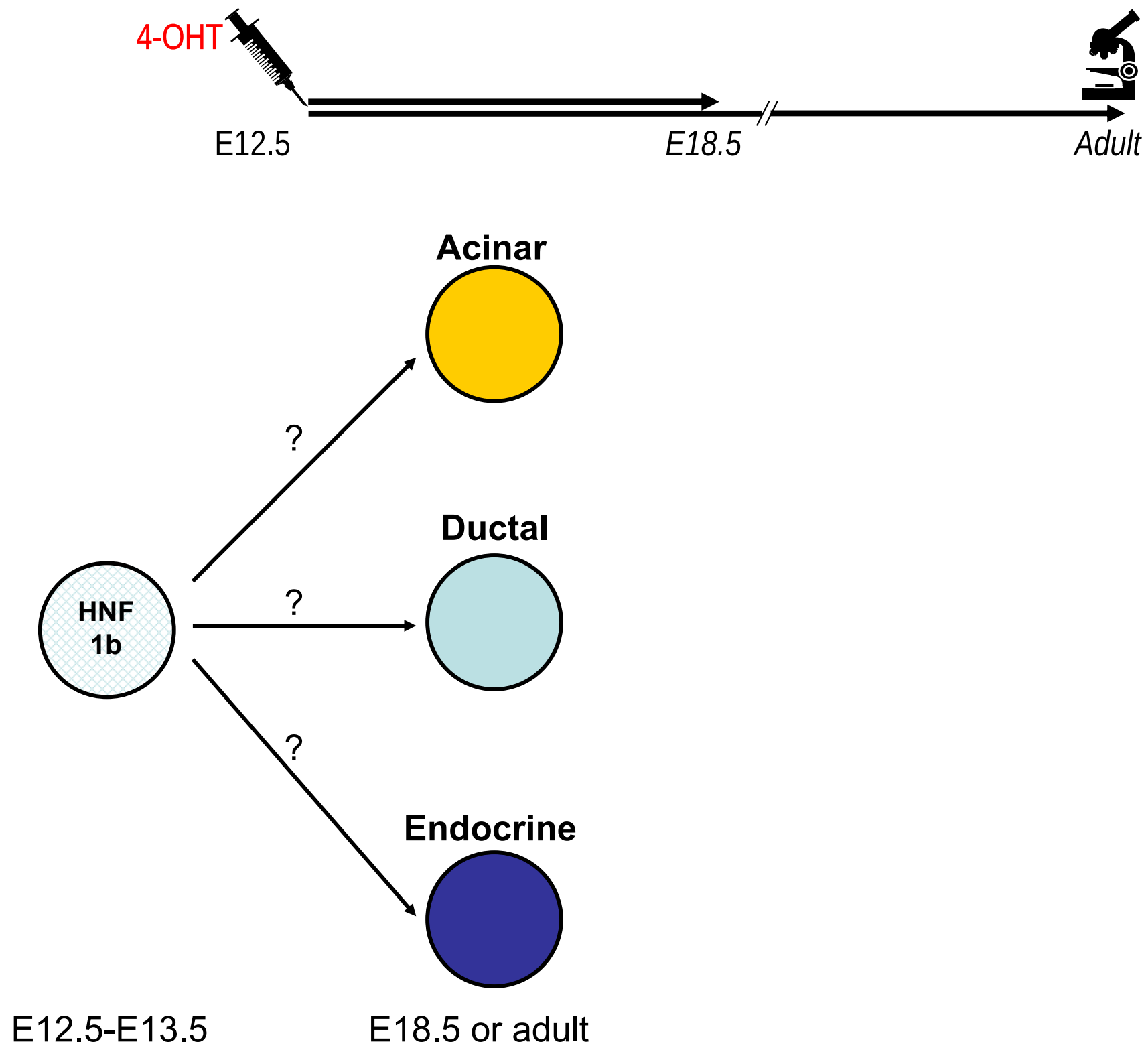


At E12.5-E13.5 CreER is expressed (like Hnf1b) in duct-like trunk cells of the developing pancreas

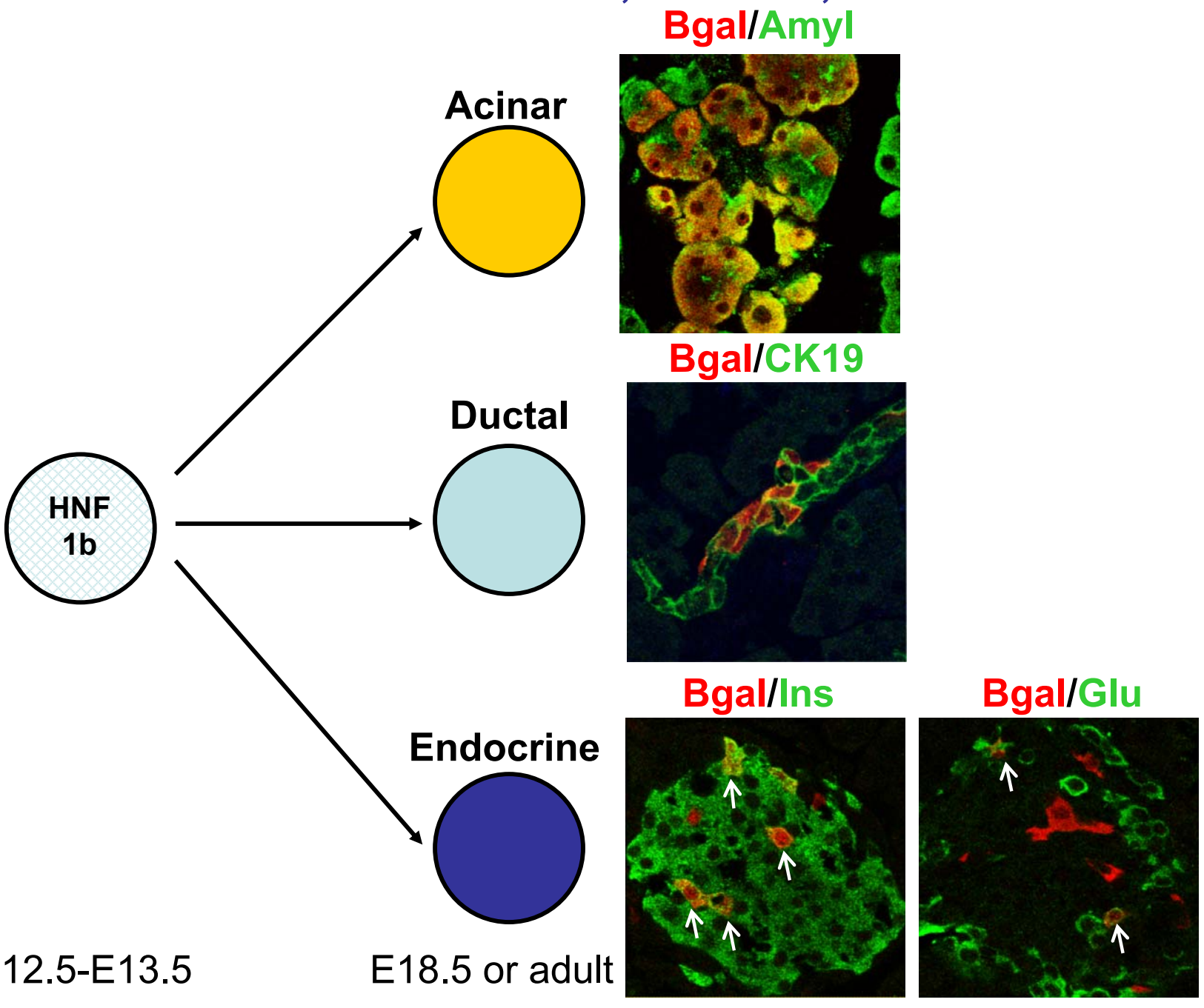
Cre/E-Cad



E12.5-noTAM **E13.5-24hTAM**

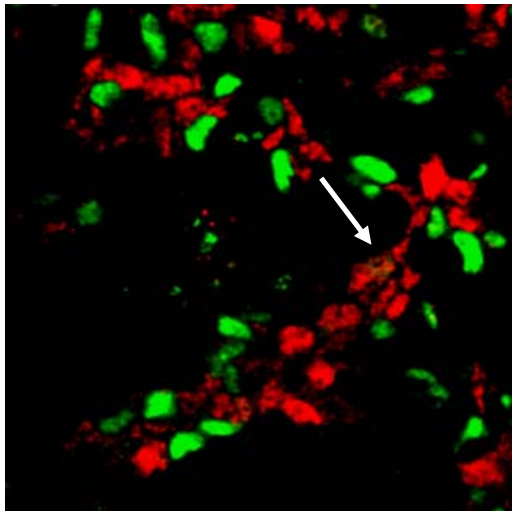

4-OHT
E12.5
E18.5
Adult
Acinar
Ductal
Endocrine
HNF
1b
?
?
?
E12.5-E13.5
E18.5 or adult

Hnf1β+ cells from E12.5-E13.5 give rise to differentiated duct, acinar, and endocrine cells

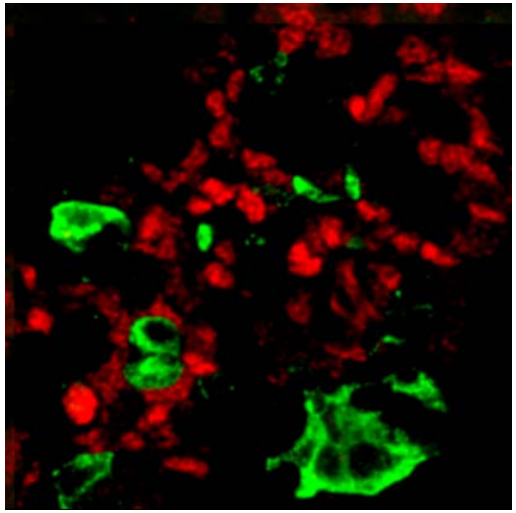


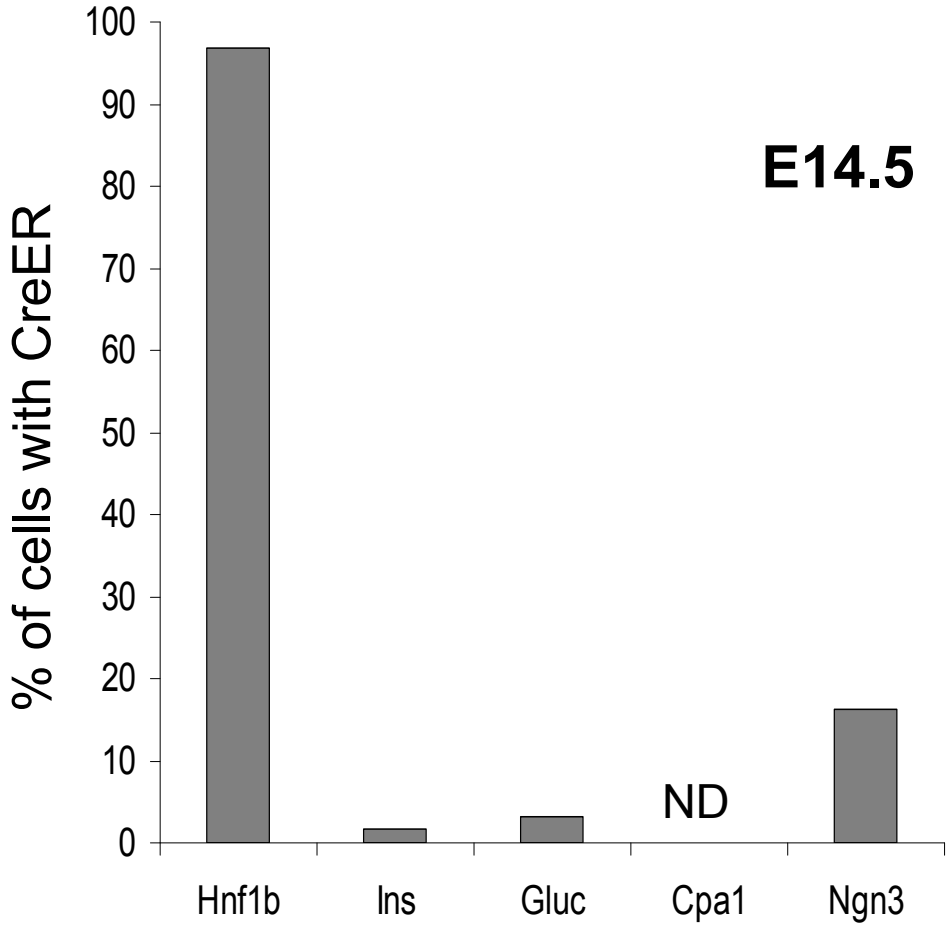
During the secondary transition (E13.5-E16.5) CreER is expressed in the ductal epithelium

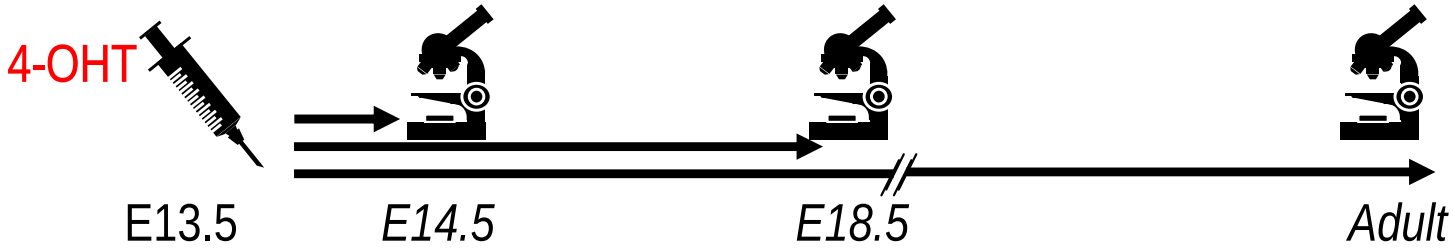
Cre/Ngn3

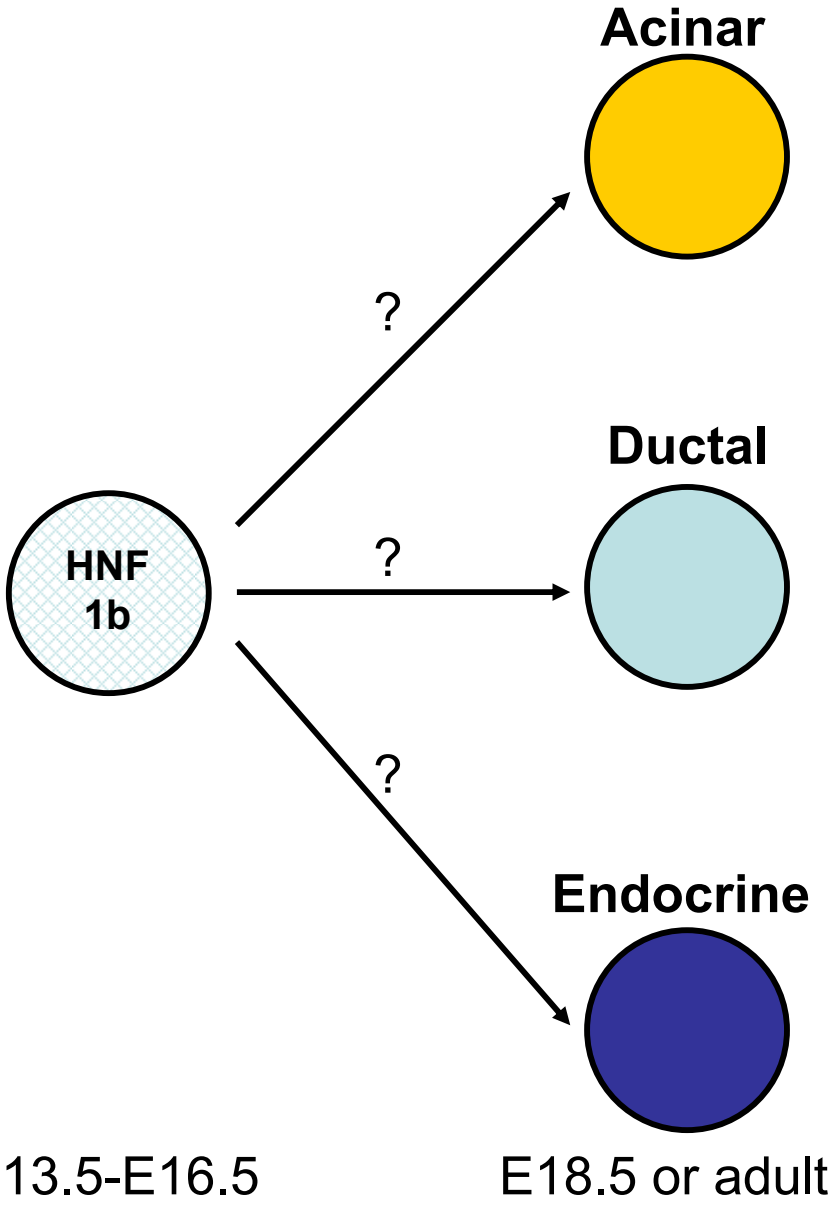


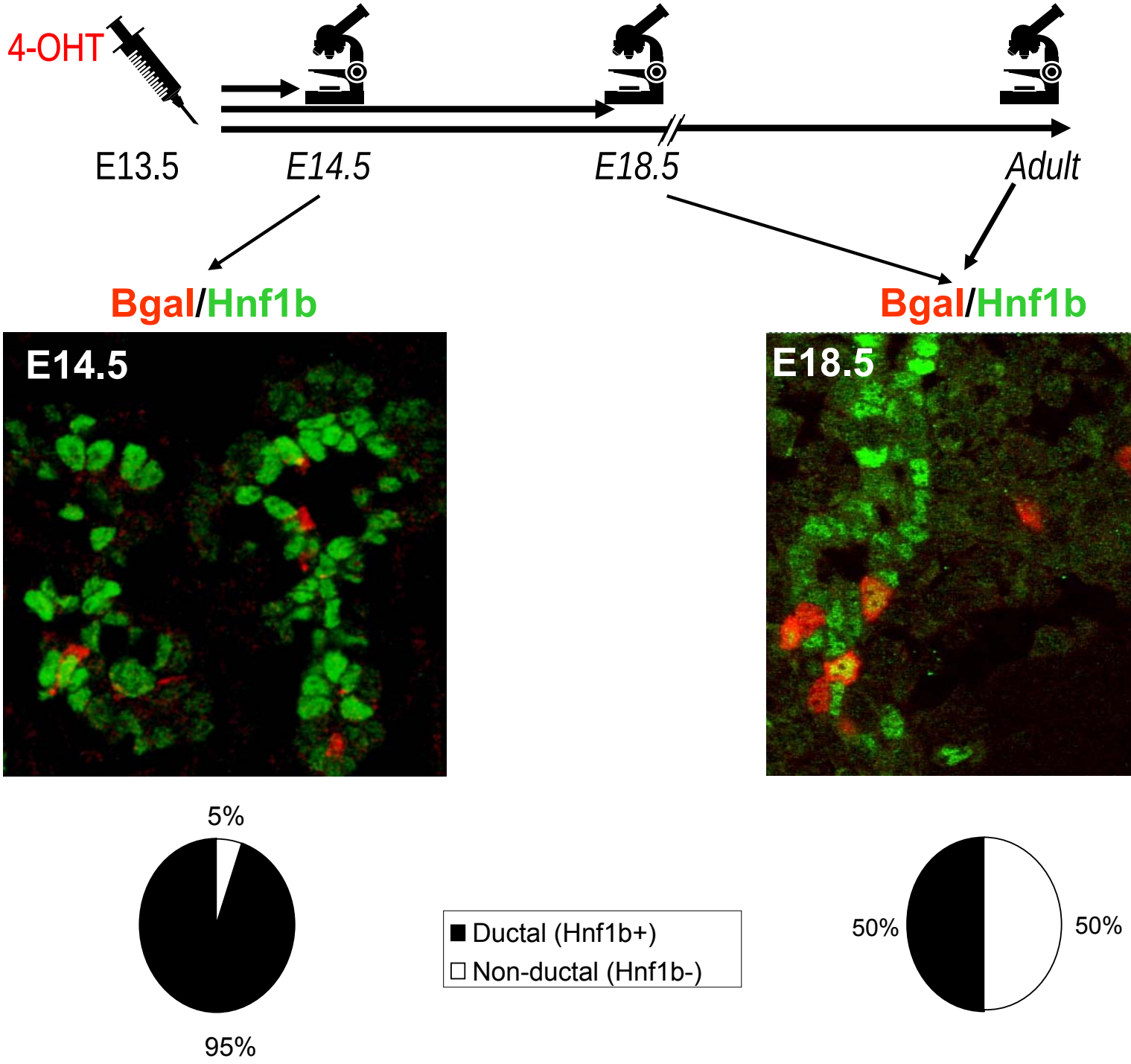
Cre/InsGlu





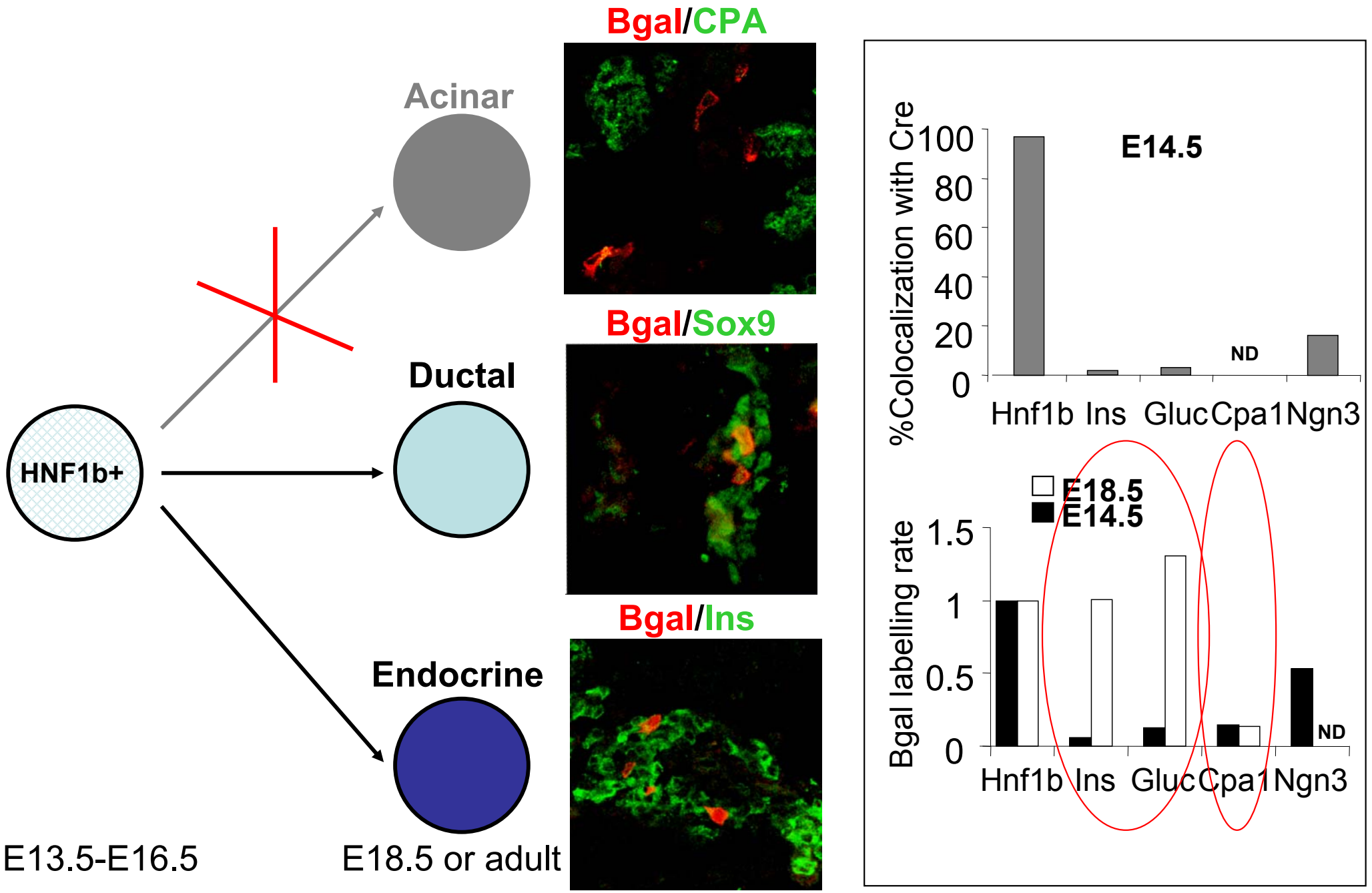

4-OHT
E13.5
E14.5
E18.5
Adult


Acinar
Ductal
Endocrine
HNF
1b
?
?
?
E13.5-E16.5
E18.5 or adult



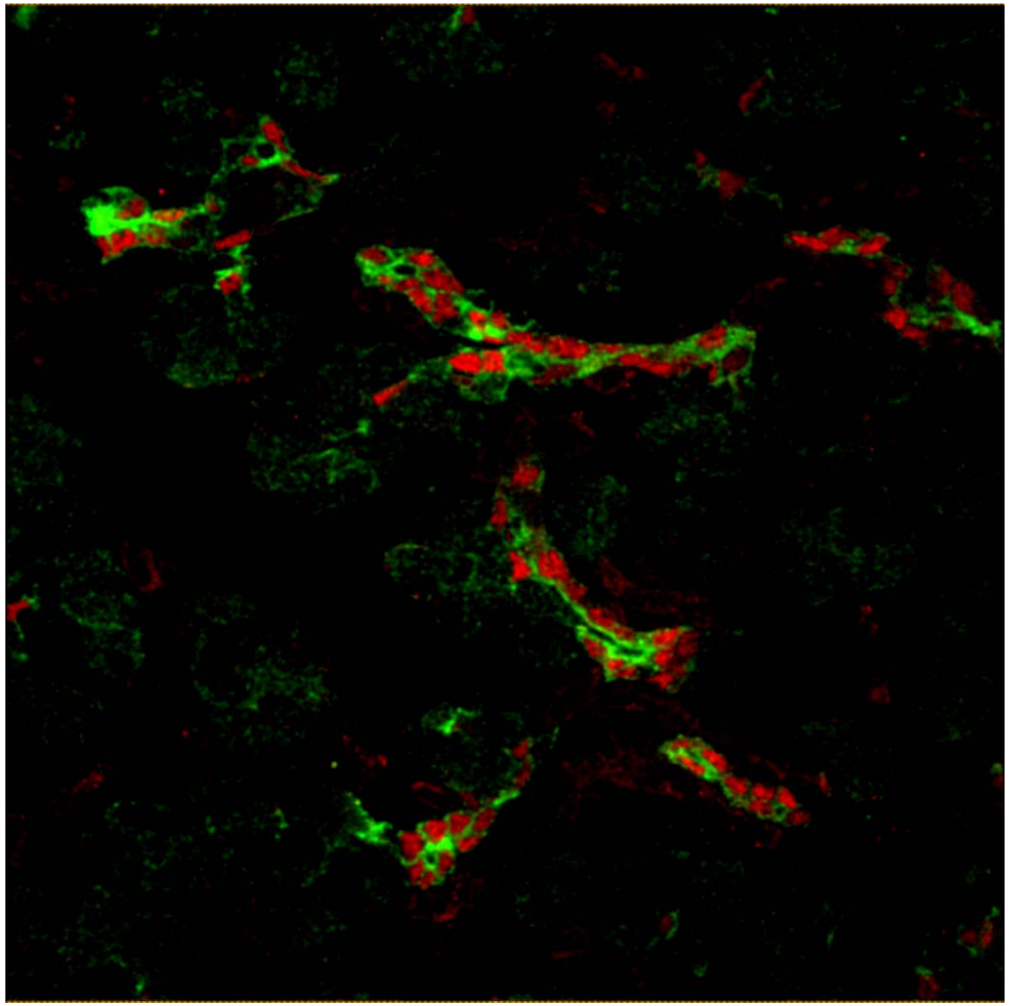
Hnf1b+ duct cells of the secondary transition give rise to non-duct cells

Duct cells from the secondary transition give rise to differentiated duct and endocrine cells

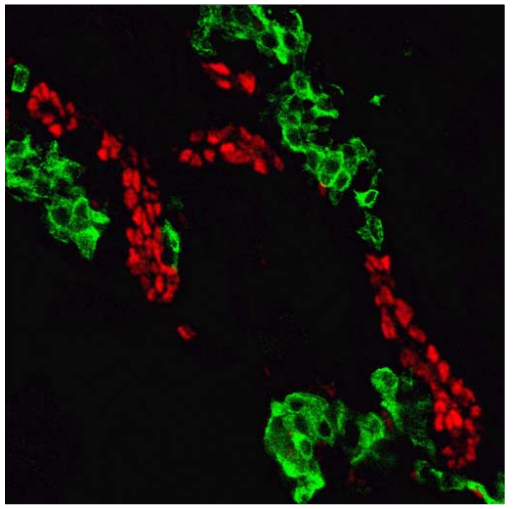


At birth CreER remains expressed broadly throughout the ductal epithelium

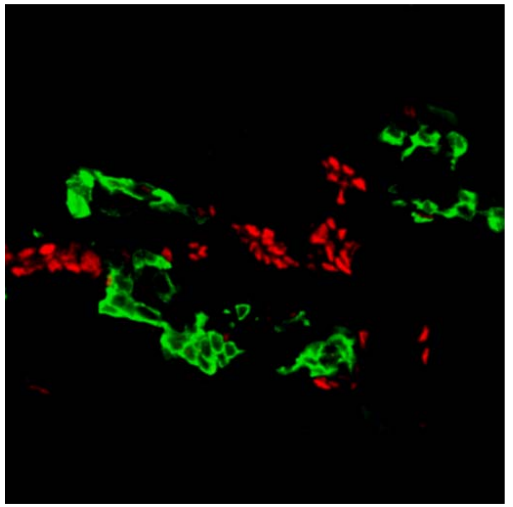
Cre/CK19

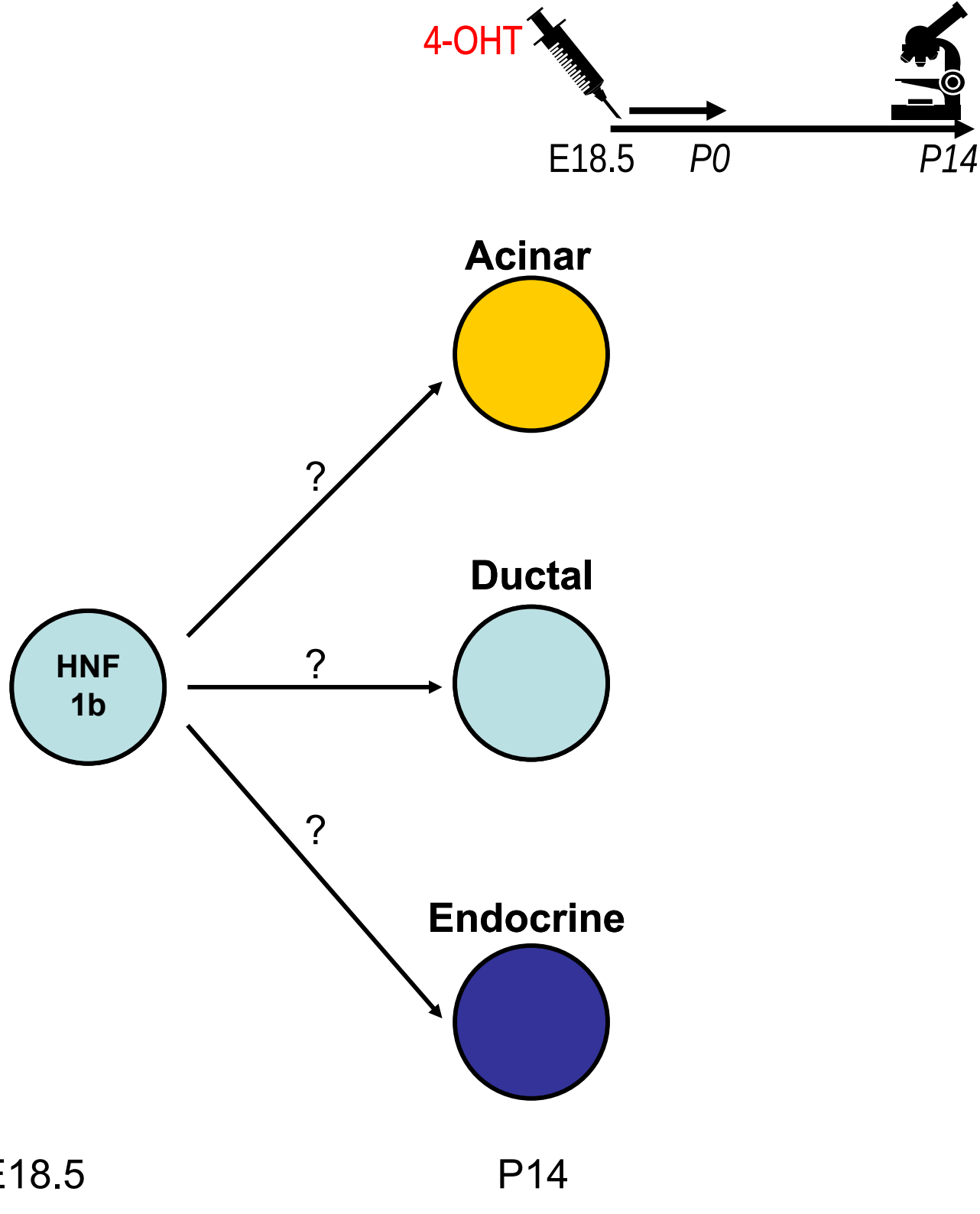


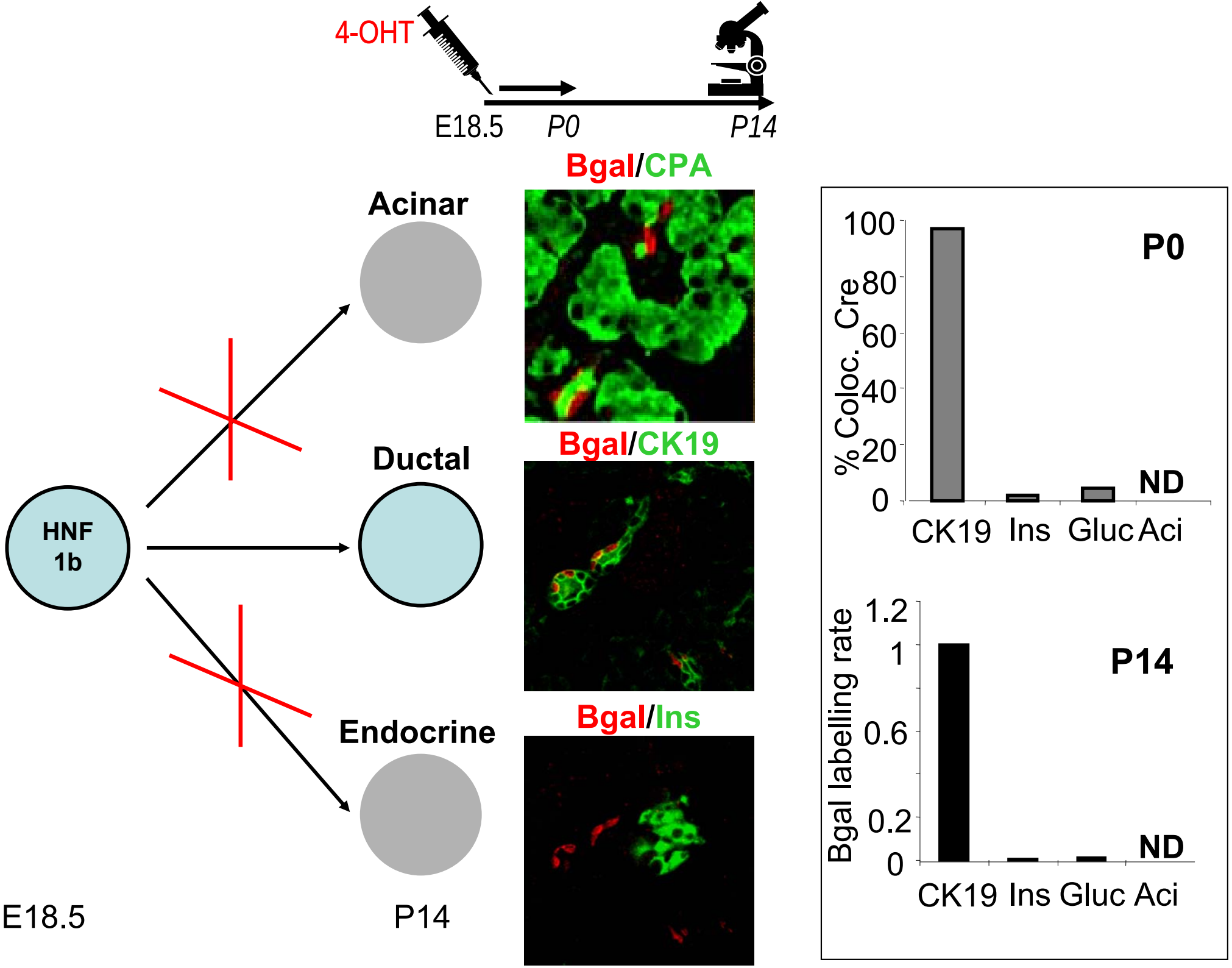
Cre/Ins



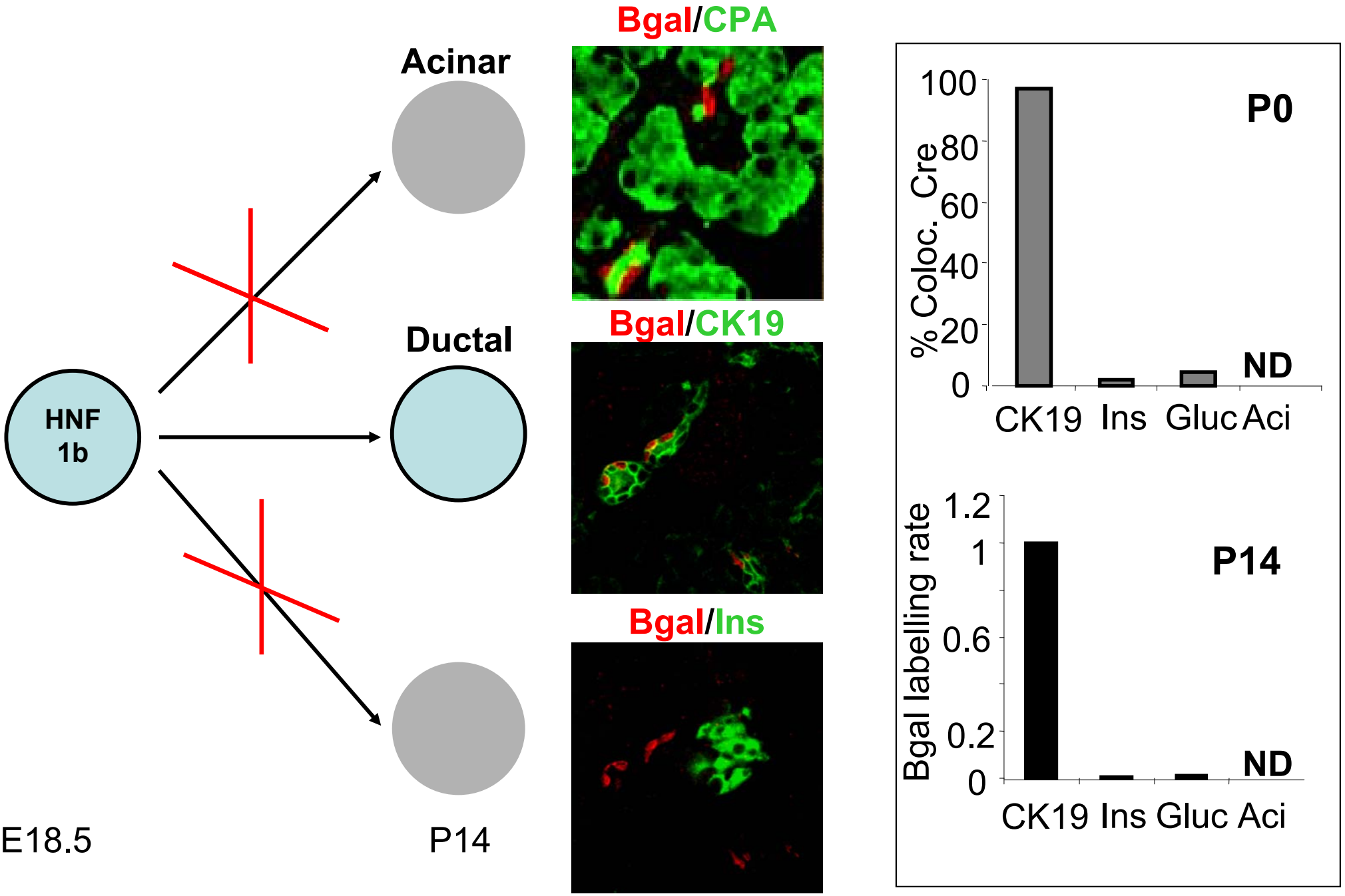
Cre/Glu



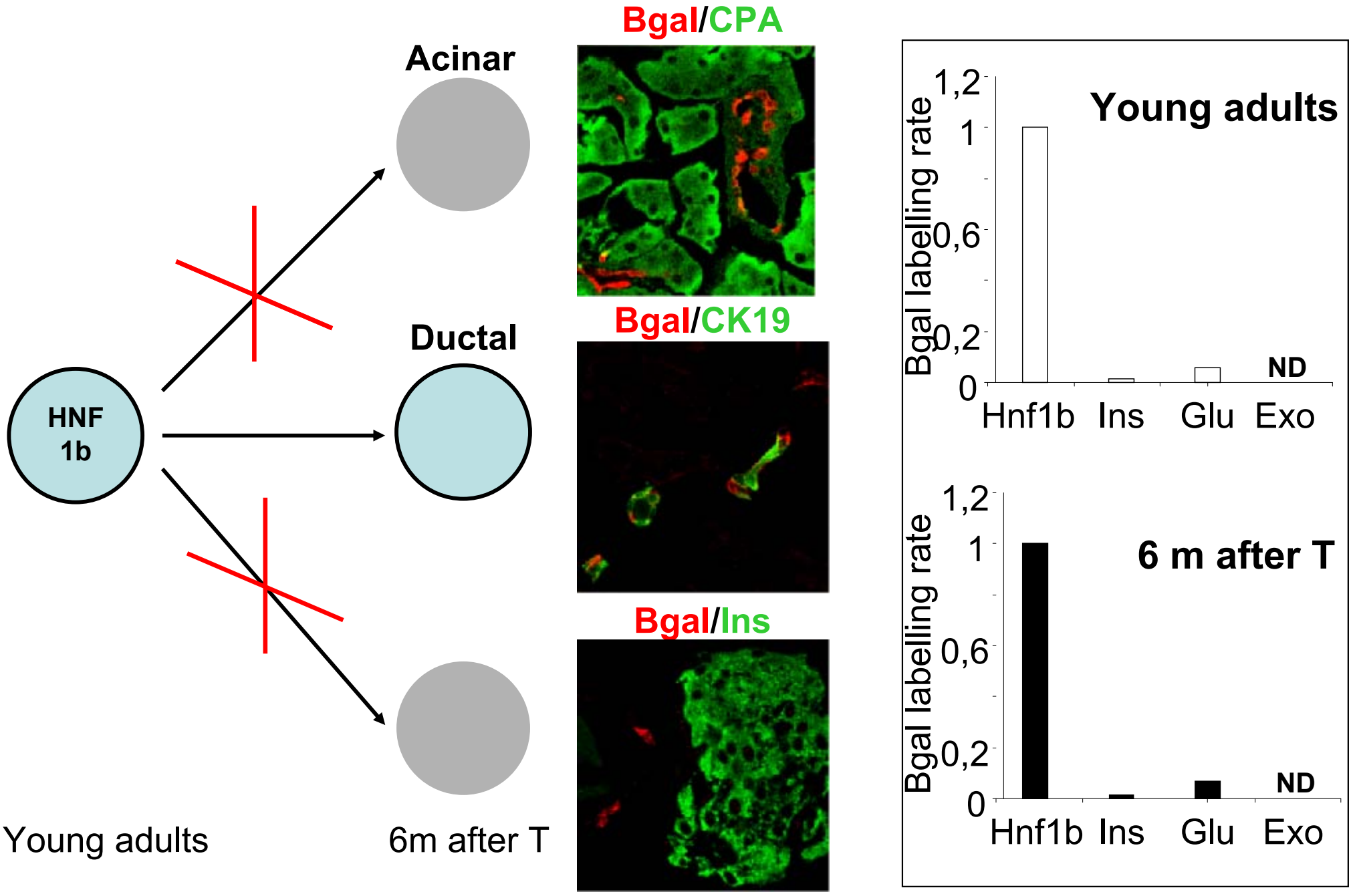

4-OHT
E18.5
P0
P14
Acinar
Ductal
Endocrine
HNF
1b
?
?
?
E18.5
P14


4-OHT
E18.5
P0
P14
Bgal/CPA
Acinar
Bgal/CK19
Ductal
HNF
1b
Bgal/Ins
Endocrine
E18.5
P14
P0
% Coloc. Cre
100
80
60
40
20
0
ND
CK19
Ins
Gluc
Aci
P14
Bgal labelling rate
1.2
1
0.6
0.2
0
ND
CK19
Ins
Gluc
Aci

Pancreatic duct cells primarily give rise to duct cells during the neonatal period.



Pancreatic duct cells primarily give rise to duct cells during adult life



Do new beta-cells that arise during regeneration originate from the pancreatic duct epithelium?

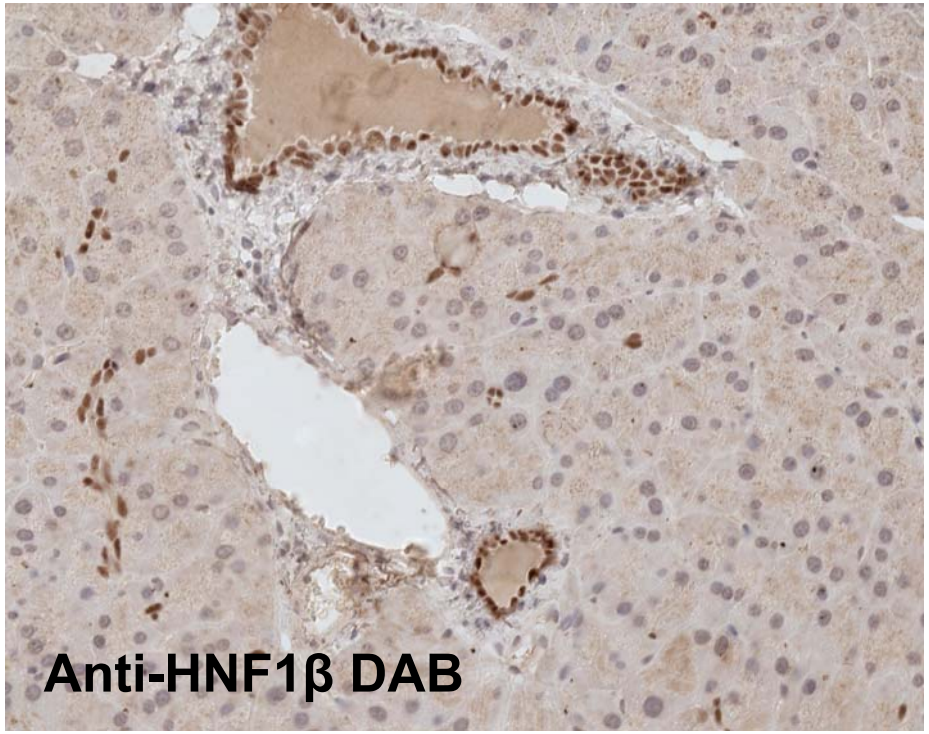
Carbonic anhydrase II-positive pancreatic cells are progenitors for both endocrine and exocrine pancreas after birth

Akari Inada[1,2], Cameron Nienaber[1], Hitoshi Katsuta[1], Yoshio Fujitani[1,2], Jared Levine[1], Rina Morita[1], Arun Sharma[1], and Susan Bonner-Weir[1,3]

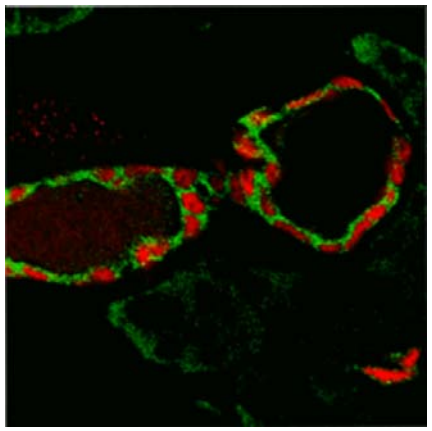
β Cells Can Be Generated from Endogenous Progenitors in Injured Adult Mouse Pancreas

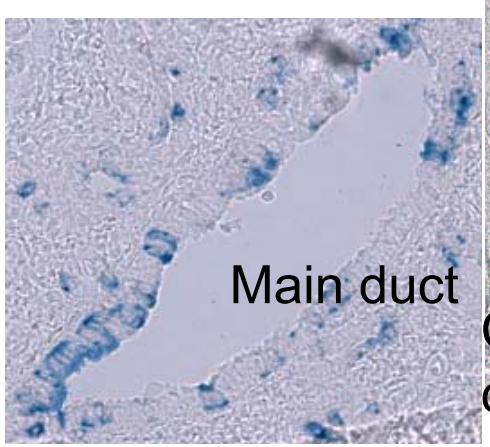
Xiaobo Xu,[1,5] Joke D'Hoker,[1,5] Geert Stangé,[1,5] Stefan Bonné,[1,5] Nico De Leu,[1,5] Xiangwei Xiao,[1,5] Mark Van De Casteele,[1,5] Georg Mellitzer,[2,5] Zhidong Ling,[1,5] Danny Pipeleers,[1,5] Luc Bouwens,[1,5] Raphael Scharfmann,[3,4,5] Gerard Gradwohl,[2,4,5] and Harry Heimberg[1,4,5,*]

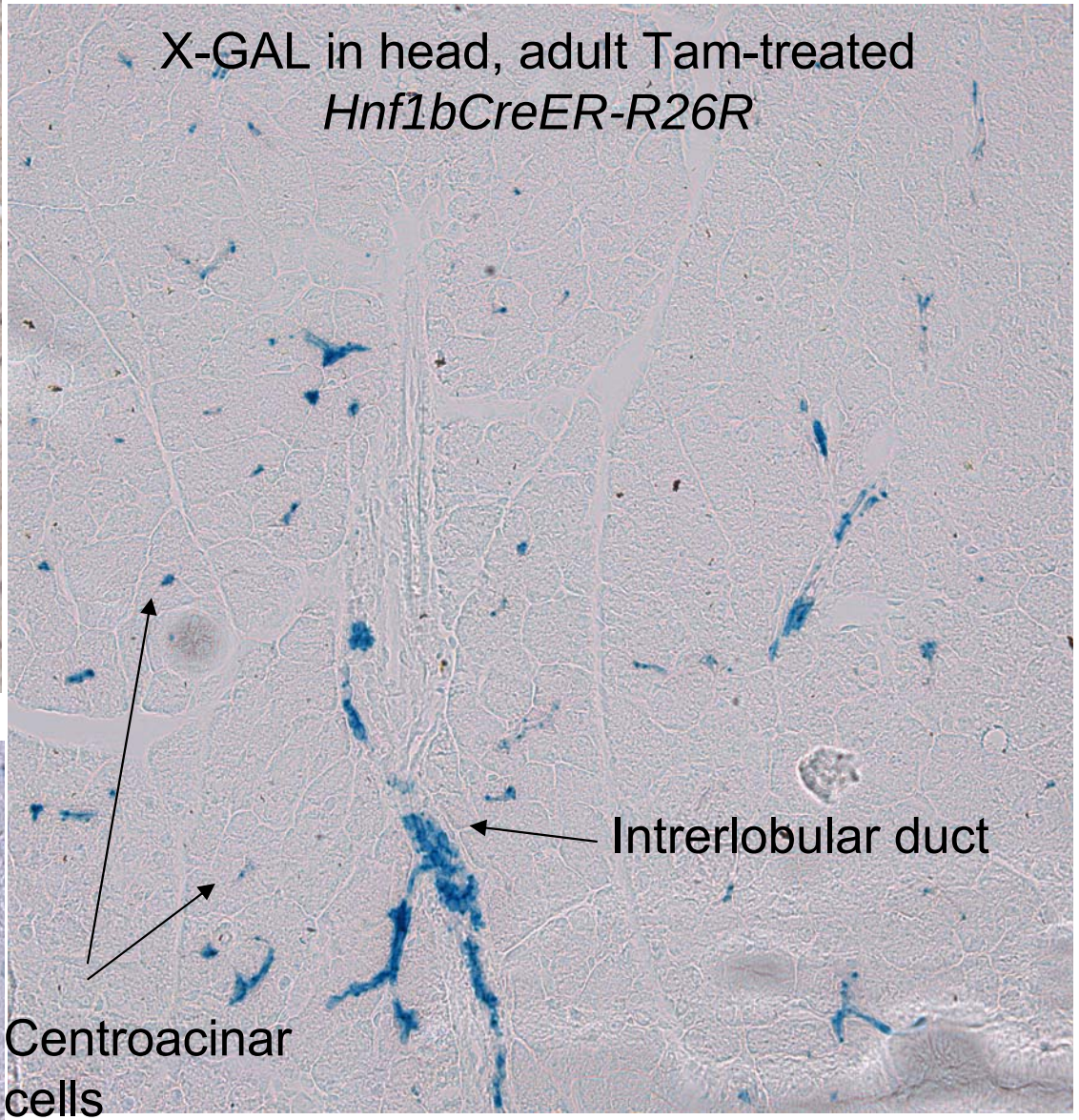
Hnf1β and *Hnf1bCreER* are widely expressed in the ductal epithelium, including main, interlobular, intralobular, intercalated, and centroacinar cells

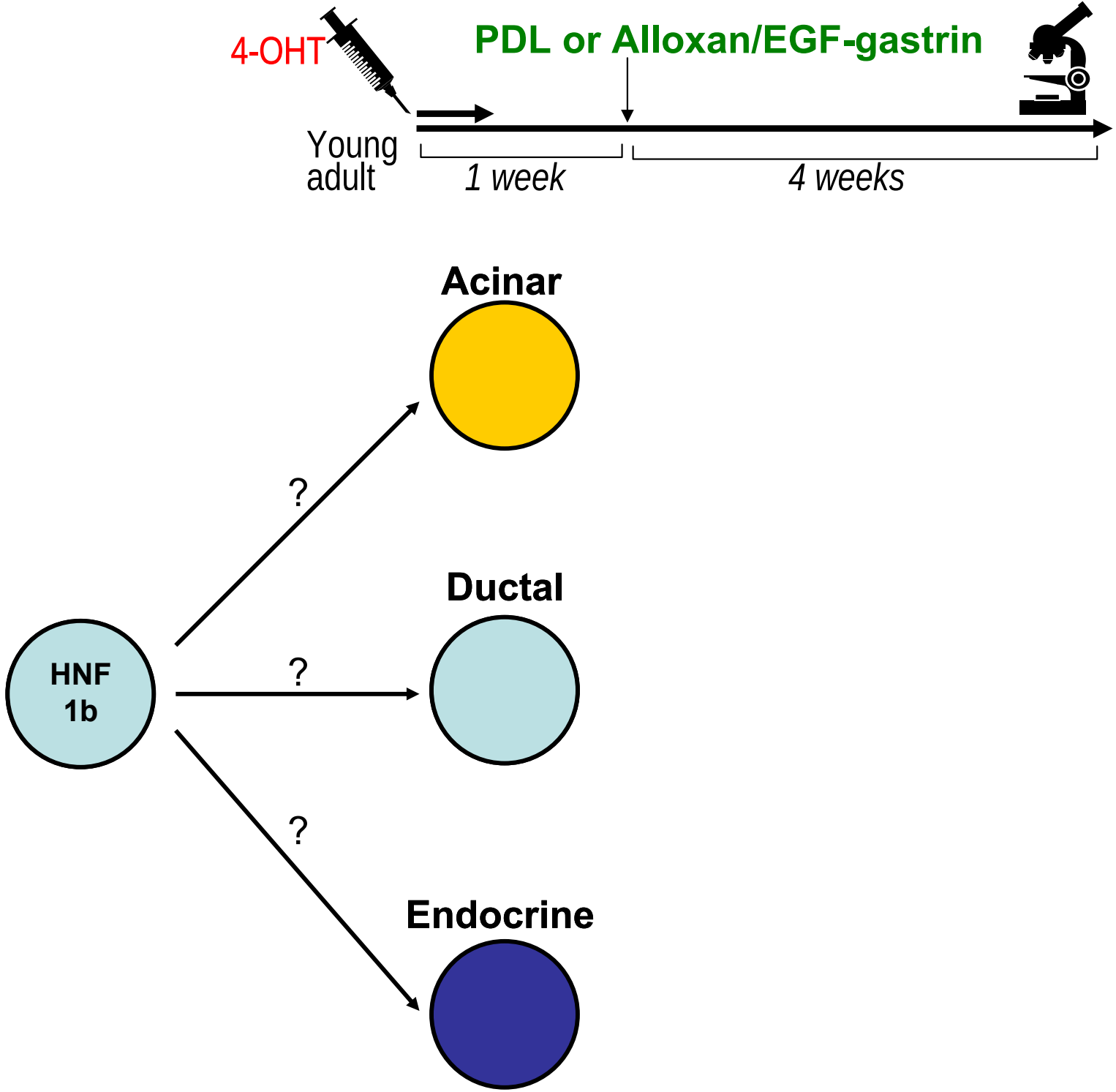


Cre/CK19

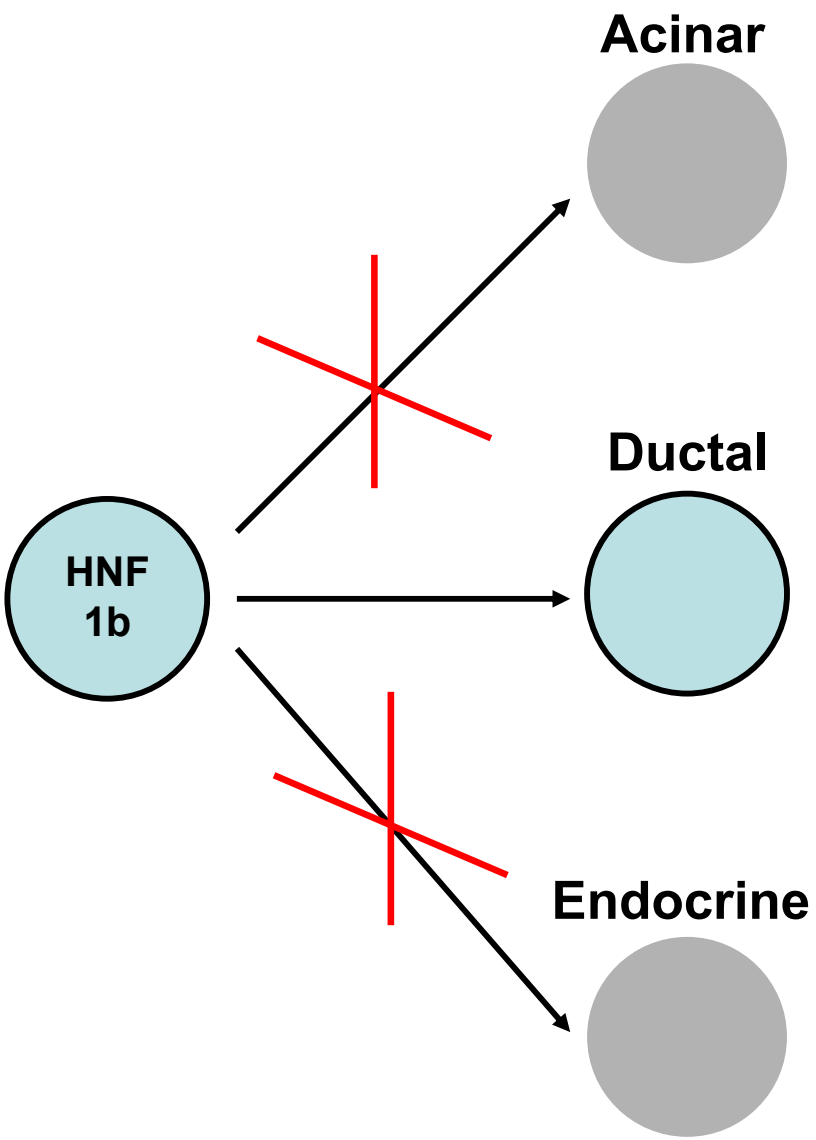




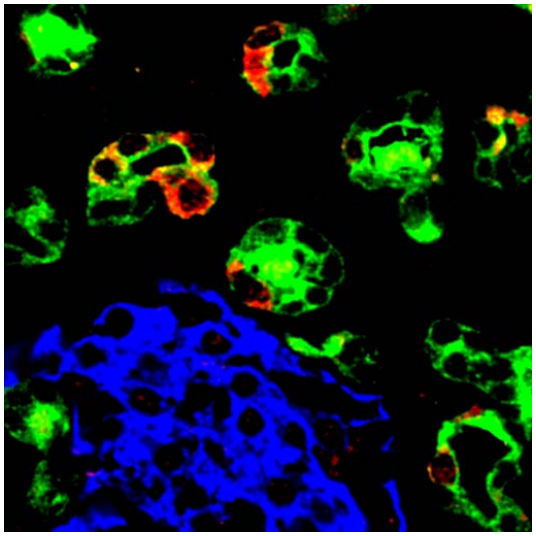



4-OHT
PDL or Alloxan/EGF-gastrin
Young adult
1 week
4 weeks
Acinar
Ductal
Endocrine
HNF 1b
?
?
?
4 weeks of age
Post-regeneration

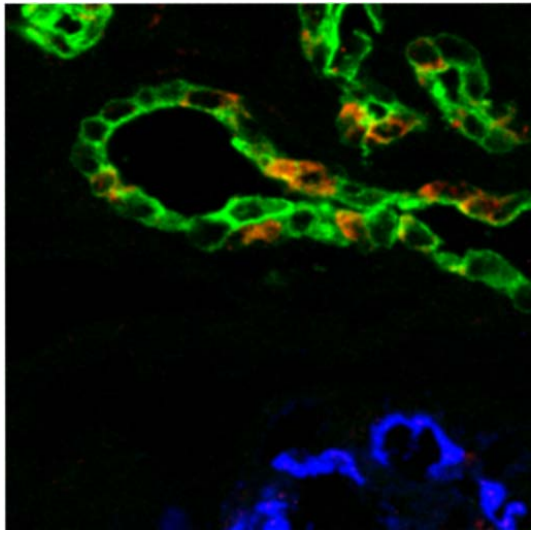
β-gal expression remains in the pancreatic duct epithelium of the ligated pancreas



Bgal/CK/Ins



Bgal/CK/Glu

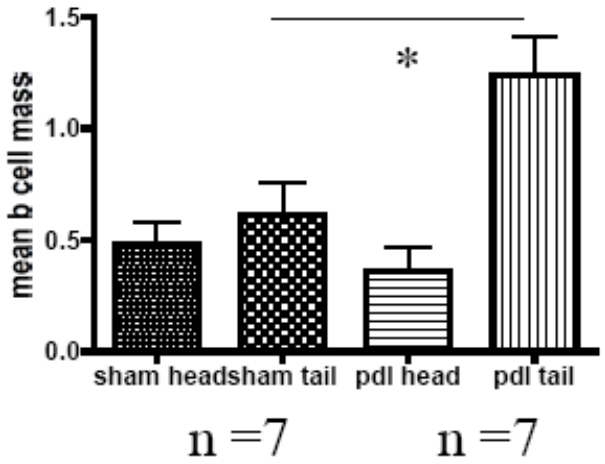


4 weeks of age

Post-regeneration

PDL causes a doubling of beta-cell mass

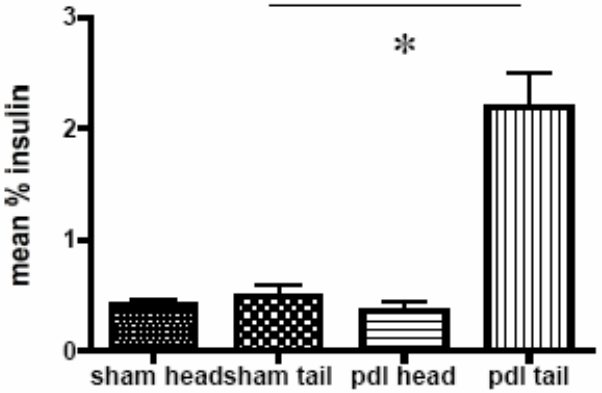
Hnf1bCreER / R26R



n =7 n =7

(*) p=0,019 unpaired t-test

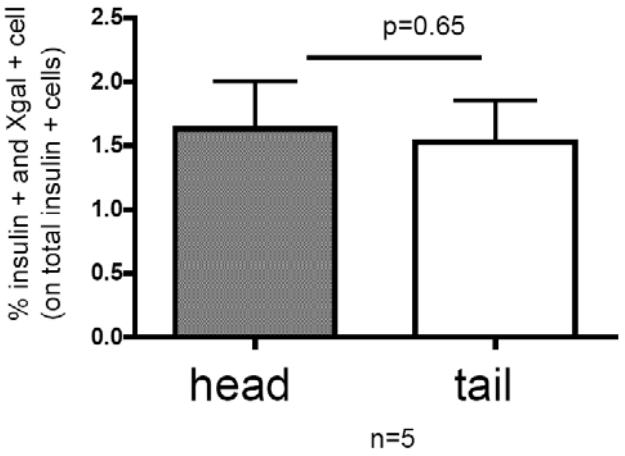
Hnf1bCreER / R26R



n =7 n =7

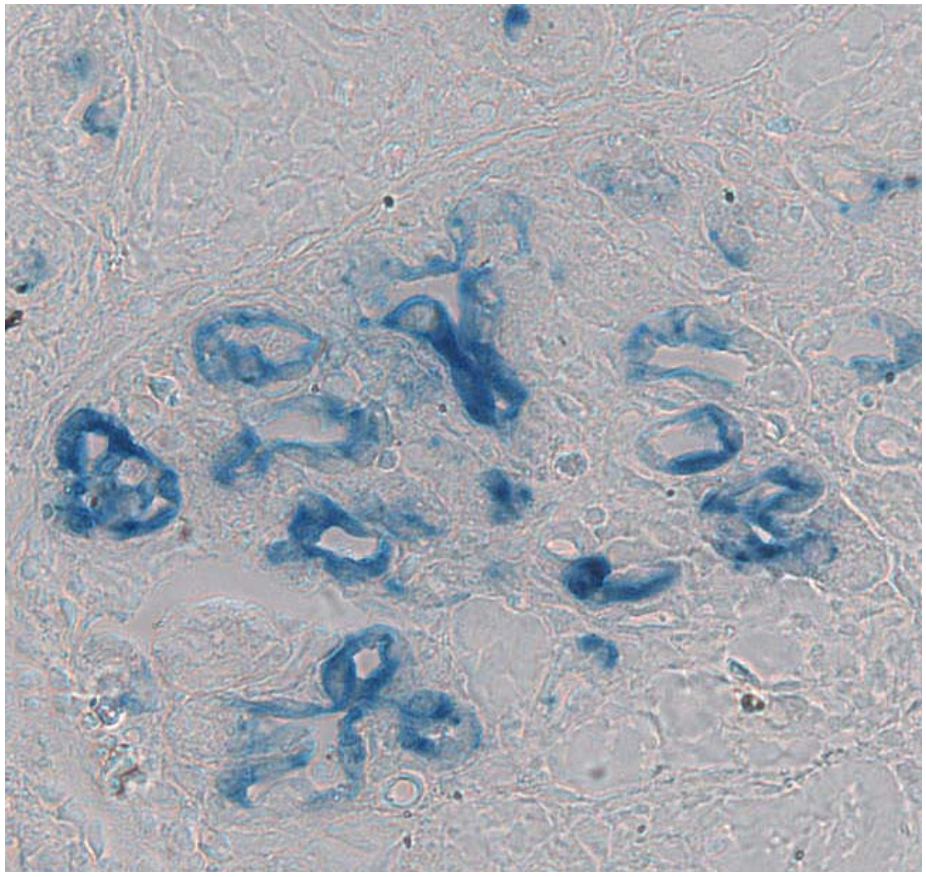
(*) p=0,0002unpaired t-test

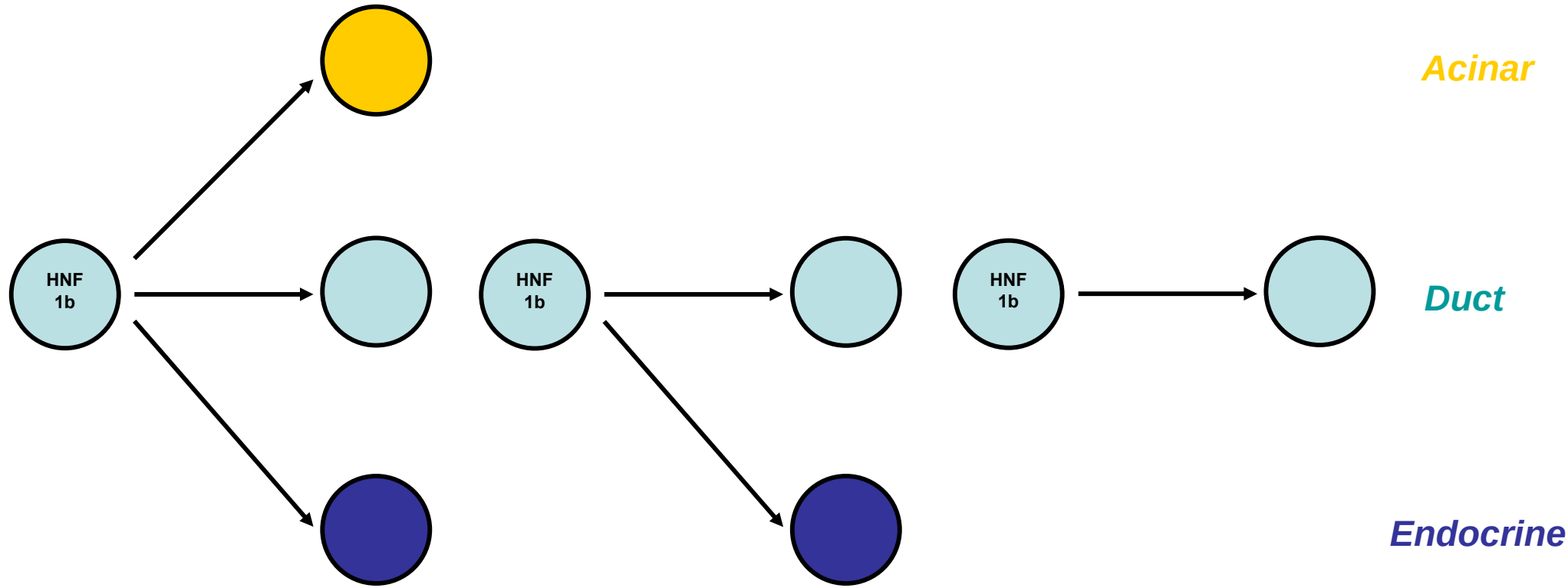
X-gal in beta-cells does not increase after PDL



Labelling efficiency in Cytoleratin+ or Hnf1b+ cells: 30-54%

Tubular complexes formed after pancreatic duct ligation are derived from pre-existing duct cells




Before E13.5
Early morphogenesis
~E13.5 –E16.5
Secondary transition
After E18.5
Physiological & regenerative growth
HNF 1b
HNF 1b
HNF 1b
Acinar
Duct
Endocrine

Aknowledgements

- Hospital Clinic/IDIBAPS
  - Mercè Martín
  - Carina Cardalda
  - Miguel Ángel Maestro
  - Vanessa Grau
  - Jorge Ferrer
- Vrije Universiteit Brussel
  - Nele de Medts
  - Isabelle Houbracken
  - Xiaobo Xu
  - Harry Heimberg
  - Luc Bouwens
- UAB transgenic core facility
  - Anna Pujol
- Reagents
  - Mike German
  - Pedro Herrera