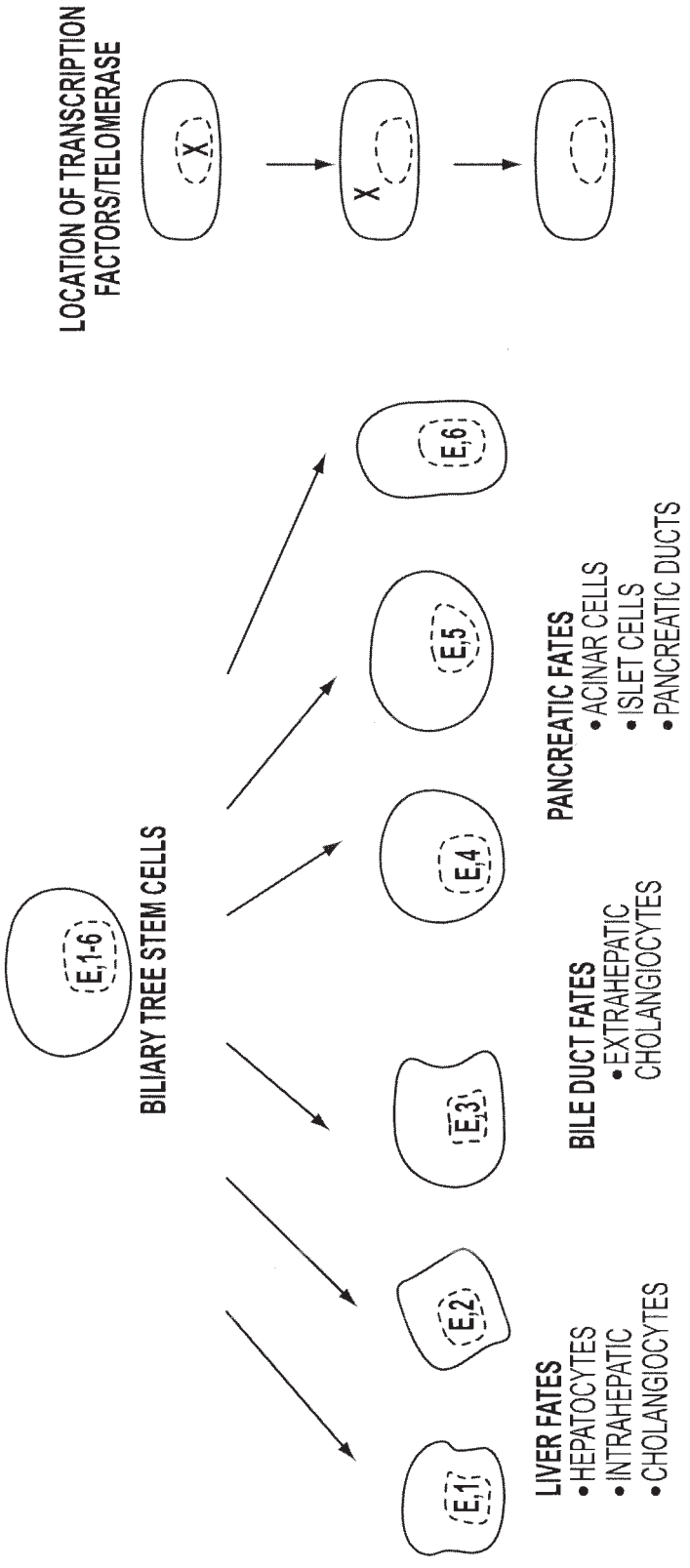

LOCATION OF TRANSCRIPTION FACTORS/TELOMERASE
X
X
BILIARY TREE STEM CELLS
E,1-6
E,1
E,2
E,3
E,4
E,5
E,6
LIVER FATES
•HEPATOCYTES
•INTRAHEPATIC
•CHOLANGIOCYTES
BILE DUCT FATES
•EXTRAHEPATIC
CHOLANGIOCYTES
PANCREATIC FATES
•ACINAR CELLS
•ISLET CELLS
•PANCREATIC DUCTS

FIG. 1

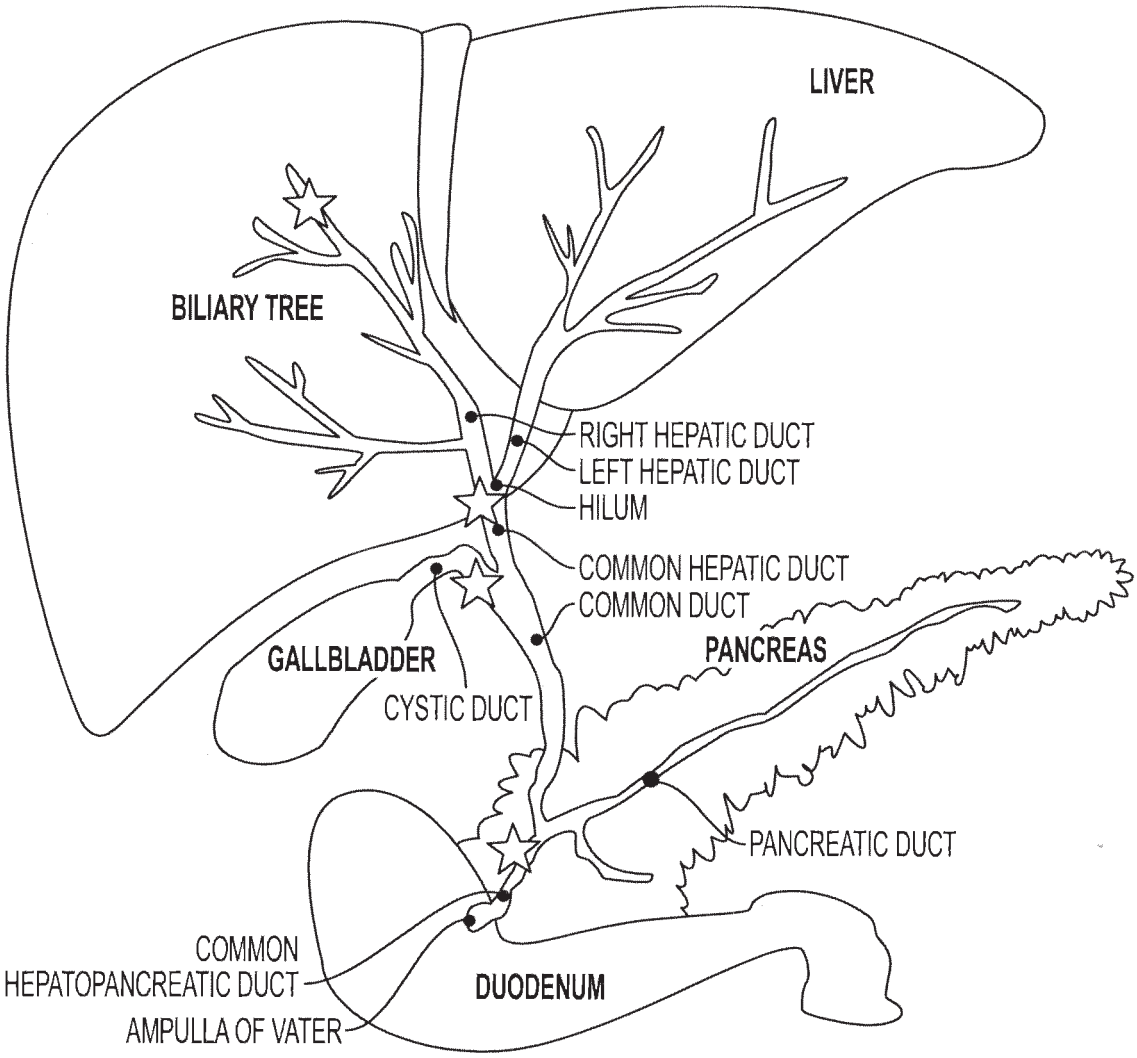
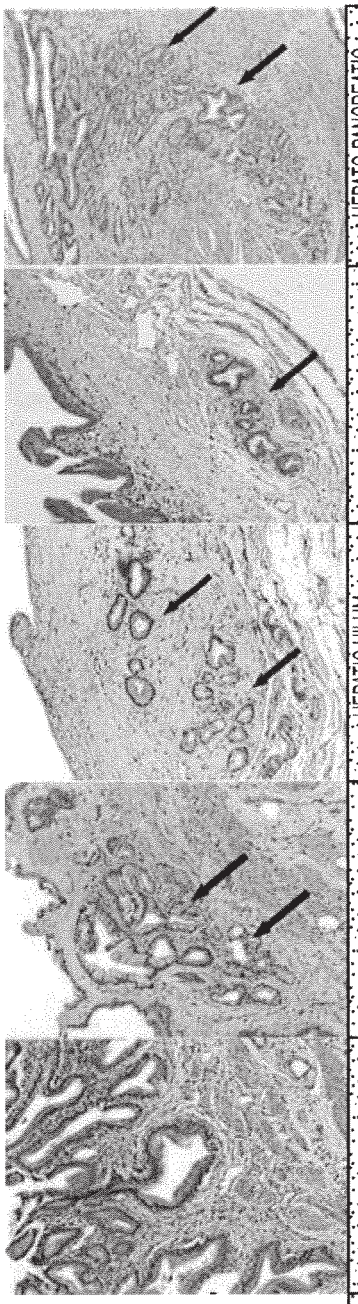

LIVER
BILIARY TREE
RIGHT HEPATIC DUCT
LEFT HEPATIC DUCT
HILUM
COMMON HEPATIC DUCT
COMMON DUCT
GALLBLADDER
CYSTIC DUCT
PANCREAS
PANCREATIC DUCT
COMMON
HEPATOPANCREATIC DUCT
AMPULLA OF VATER
DUODENUM

FIG. 2



EXTRAHEPATIC BILIARY TREE (N=5)	GALLBLADDER	CYSTIC DUCT	HEPATIC HILUM (COMMON HEPATIC DUCT)	BILE DUCT	HEPATO-PANCREATIC AMPULLA
SURFACE OCCUPIED BY PBGs (%)	/	3.22 ± 0.87 (0.39)	3.68 ± 0.79 (0.35)	1.29 ± 0.37 (0.16)*	7.47 ± 2.20 (0.98)*
AVERAGE NUMBER OF PBGs/ FIELD (20x)	/	8.15 ± 2.03 (0.91)	10.25 ± 2.27 (1.01)	4.37 ± 1.15 (0.51)*	27.83 ± 3.16 (1.41)*
AVERAGE CIRCUMFERENCE OF PBGs (μm)	/	115.07 ± 9.11 (4.07)	106.44 ± 19.79 (8.85)	101.01 ± 10.44 (4.67)	130.95 ± 14.22 (6.36)*

FIG. 3a

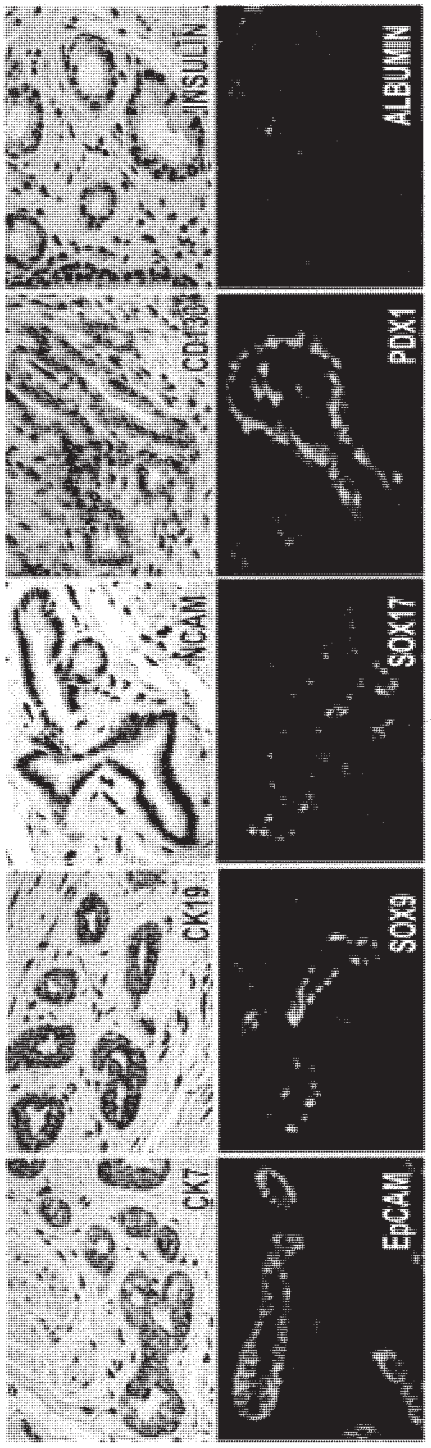


FIG. 3b

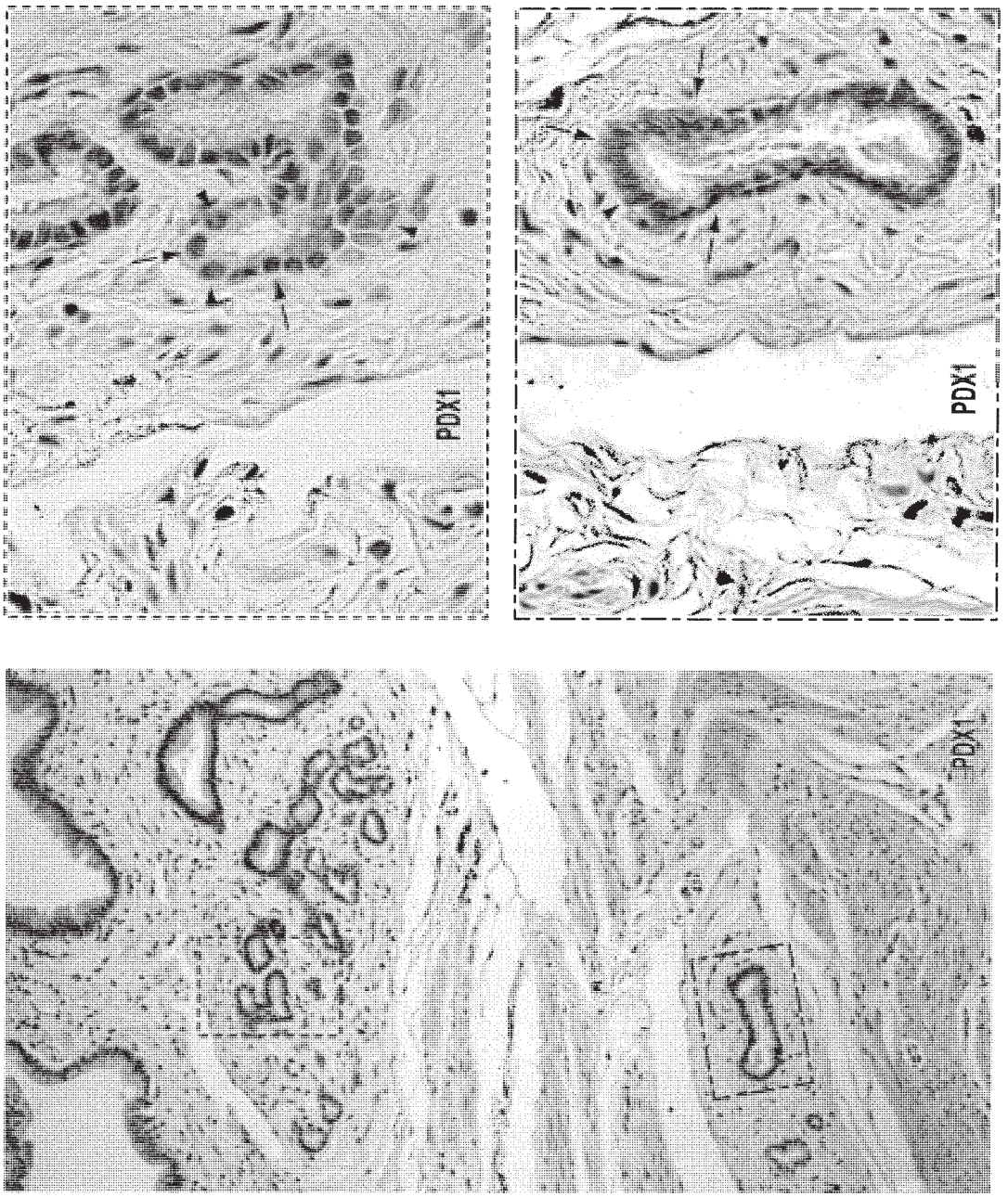


FIG. 4

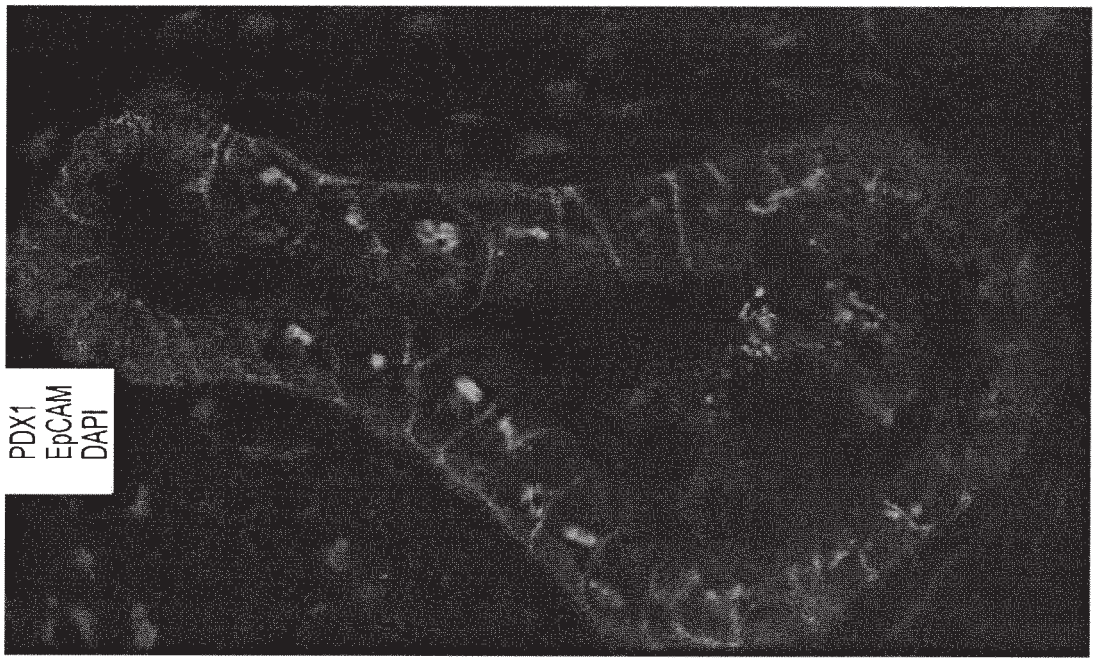


FIG. 5b

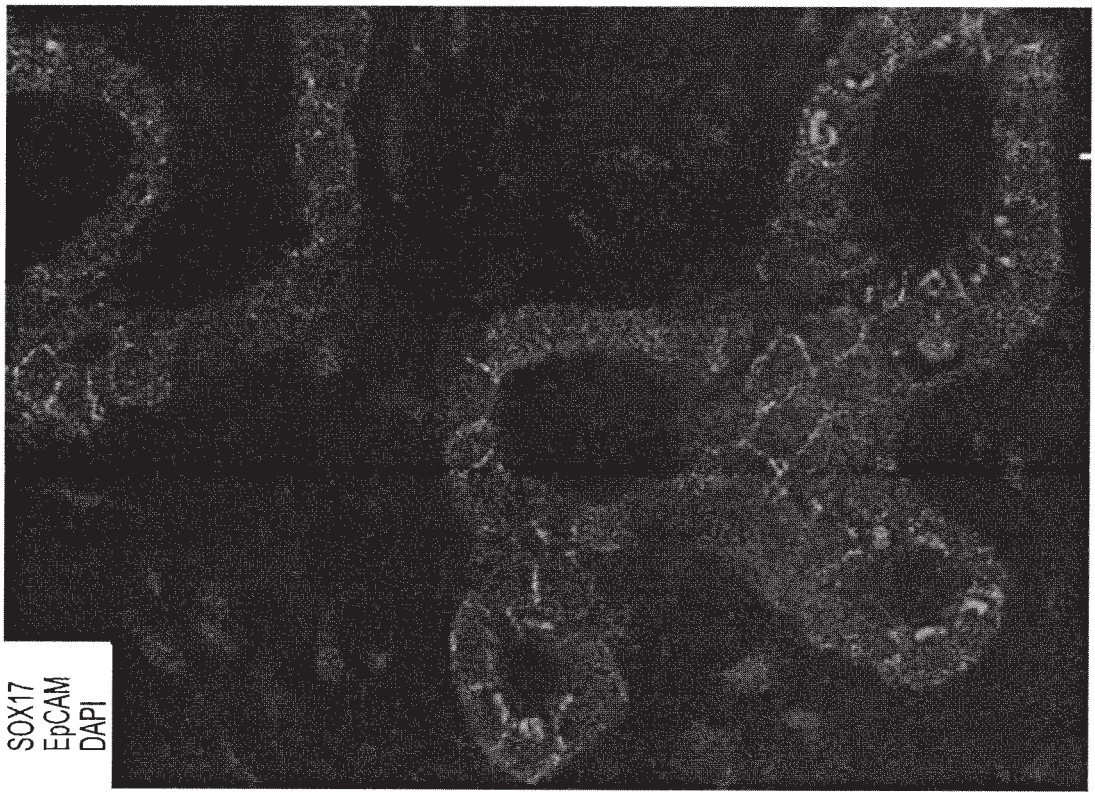


FIG. 5a

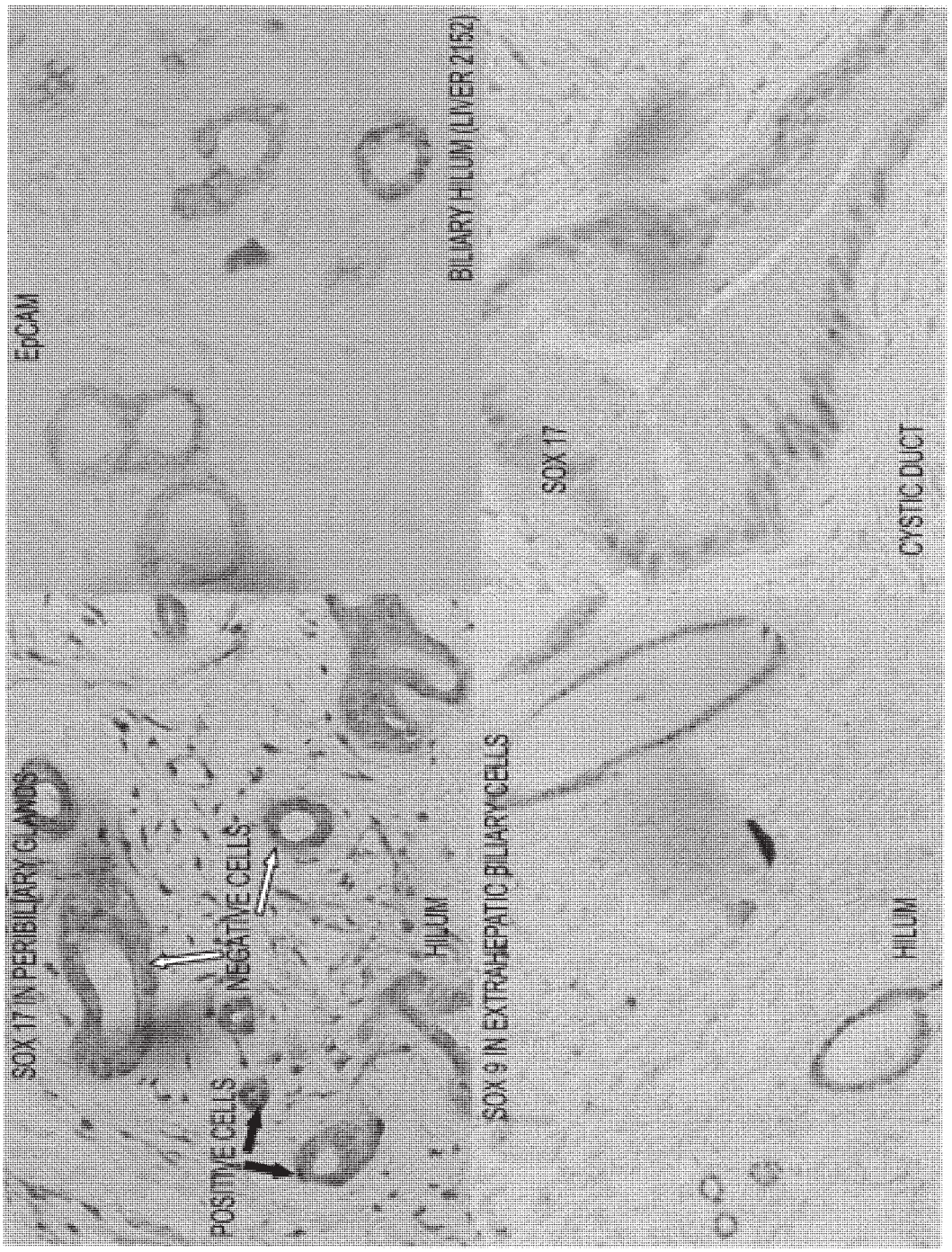

EpCAM
BILIARY-HILUM (LIVER 2152)
SOX 17 IN PERIBILIARY GLANDS
POSITIVE CELLS
NEGATIVE CELLS
HILUM
SOX 9 IN EXTRAHEPATIC BILIARY CELLS
SOX 17
CYSTIC DUCT
HILUM

FIG. 6

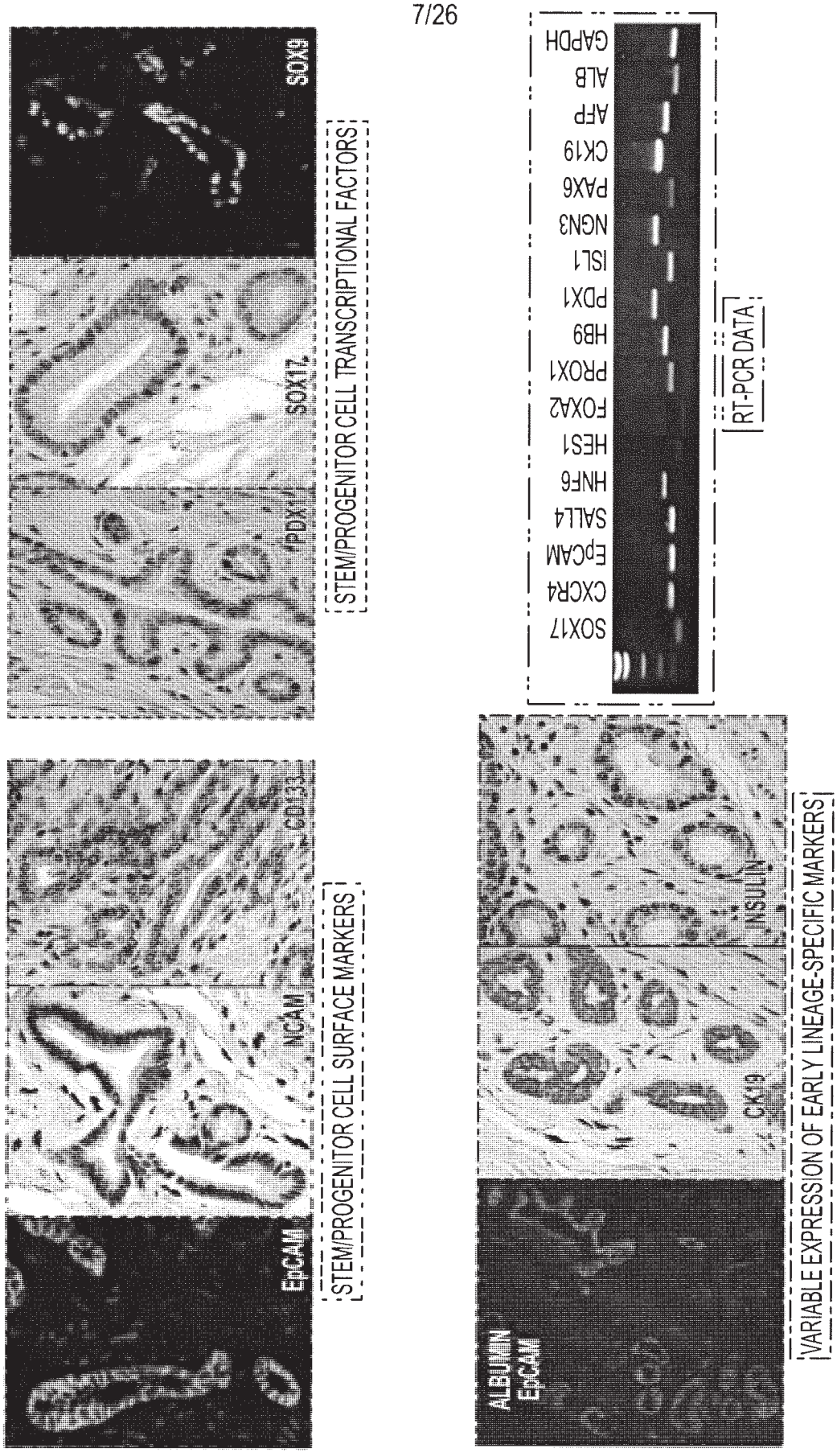

EpCAM
NCAM
CD133
STEM/PROGENITOR CELL SURFACE MARKERS
PDX1
SOX17
SOX9
STEM/PROGENITOR CELL TRANSCRIPTIONAL FACTORS
ALBUMIN
EpCAM
CK19
INSULIN
VARIABLE EXPRESSION OF EARLY LINEAGE-SPECIFIC MARKERS
SOX17
CXCR4
EpCAM
SALL4
HNF6
HES1
FOXA2
PROX1
HB9
PDX1
ISL1
NGN3
PAX6
CK19
AFP
ALB
GAPDH
RT-PCR DATA

FIG. 7

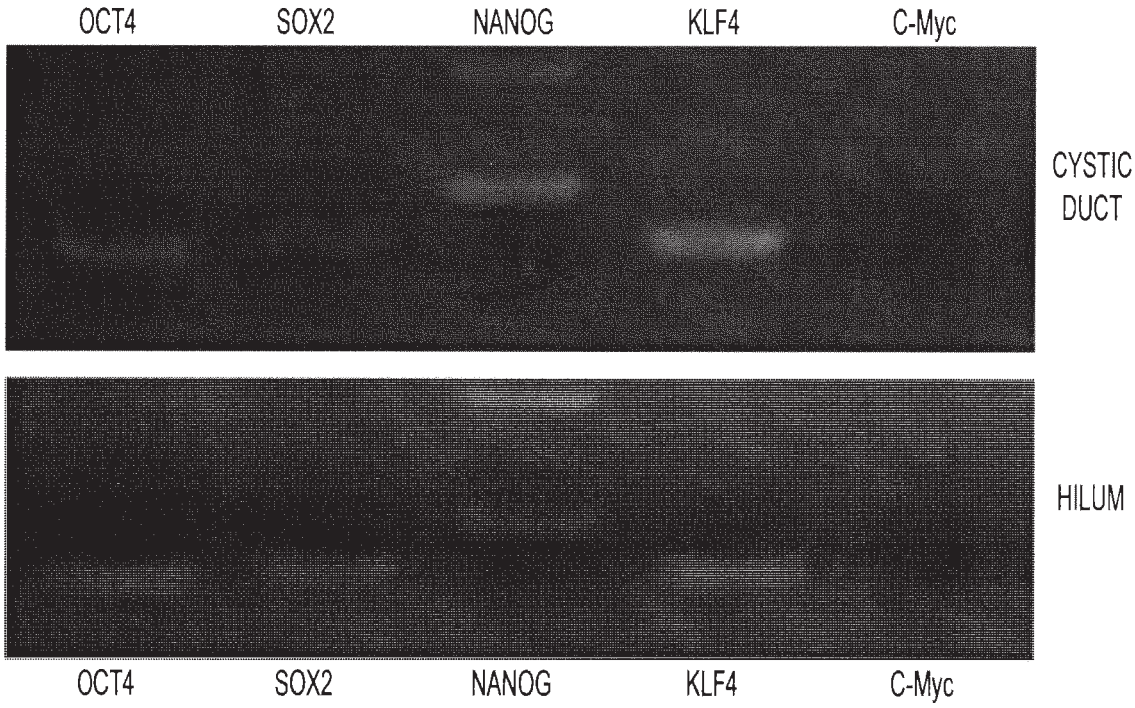

OCT4
SOX2
NANOG
KLF4
C-Myc
CYSTIC DUCT
HILUM
OCT4
SOX2
NANOG
KLF4
C-Myc

FIG. 8

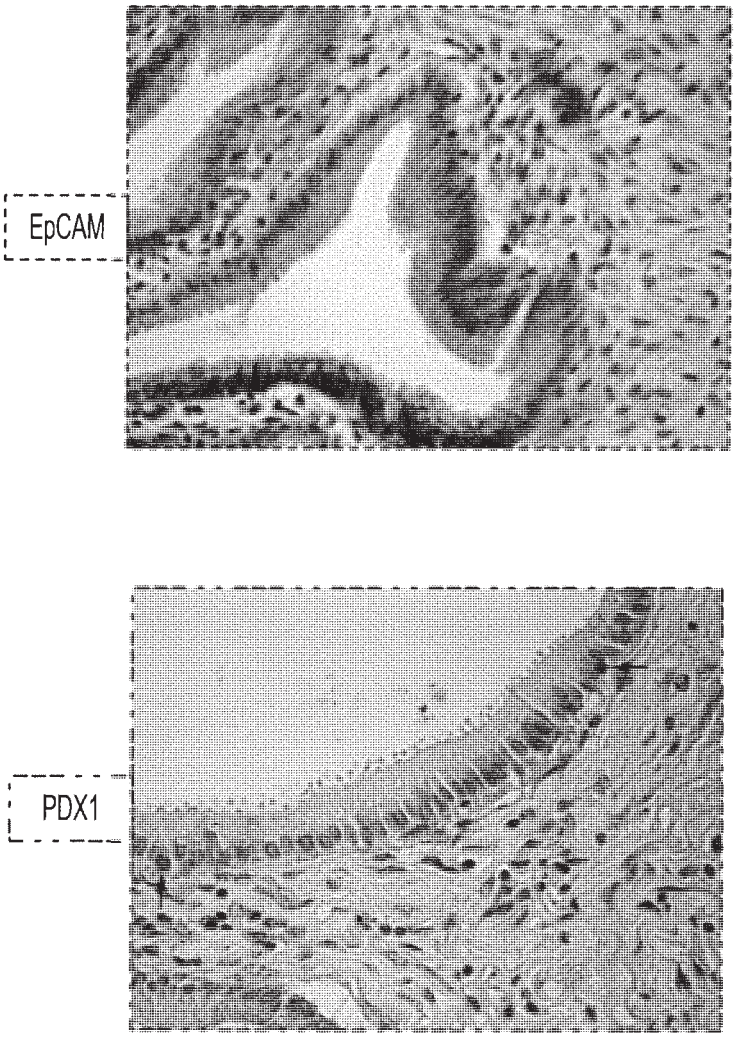


FIG. 9

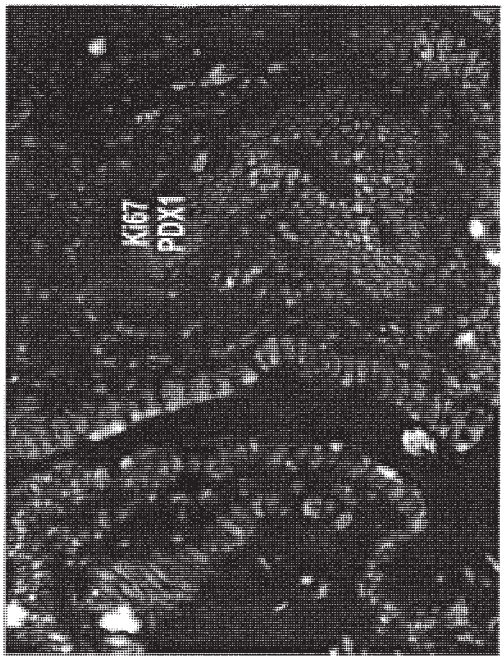


FIG. 10b



FIG. 10d

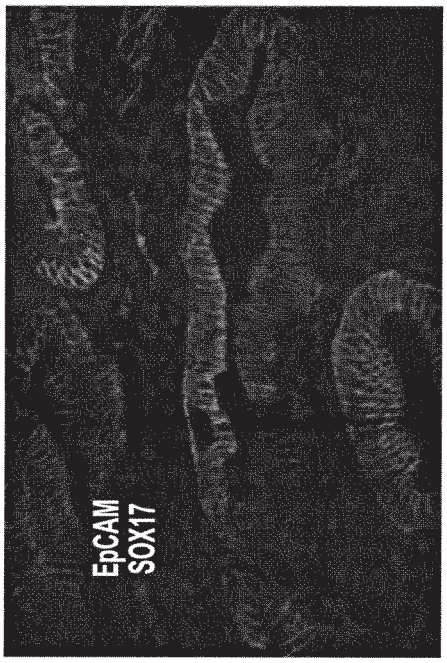


FIG. 10a

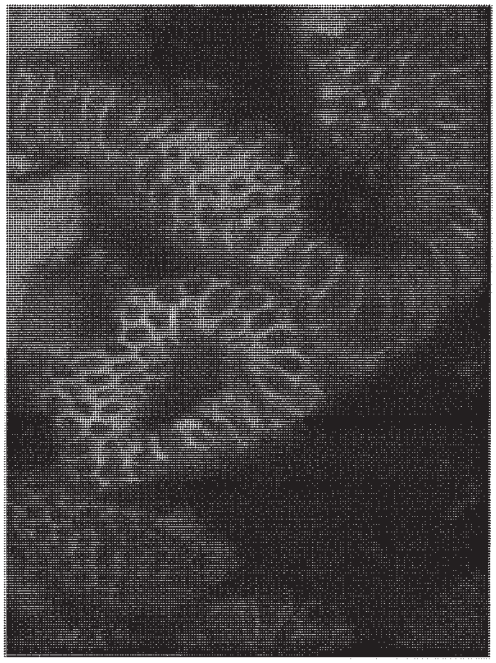


FIG. 10c

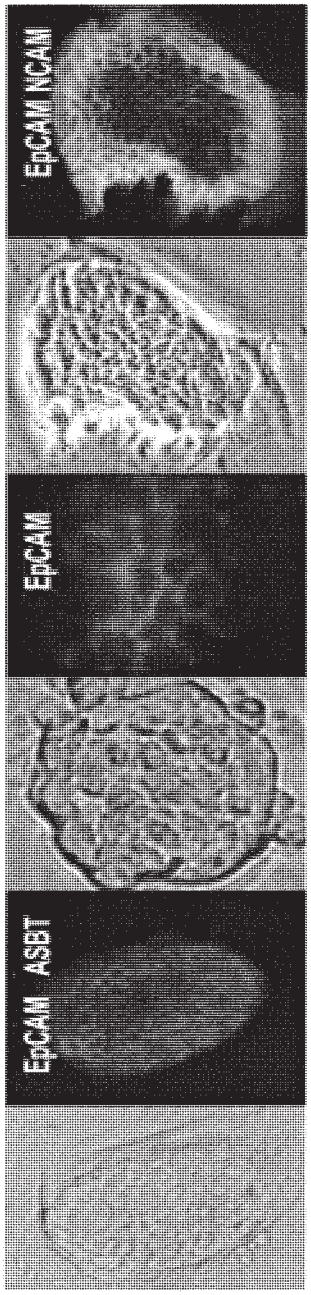


FIG. 11a

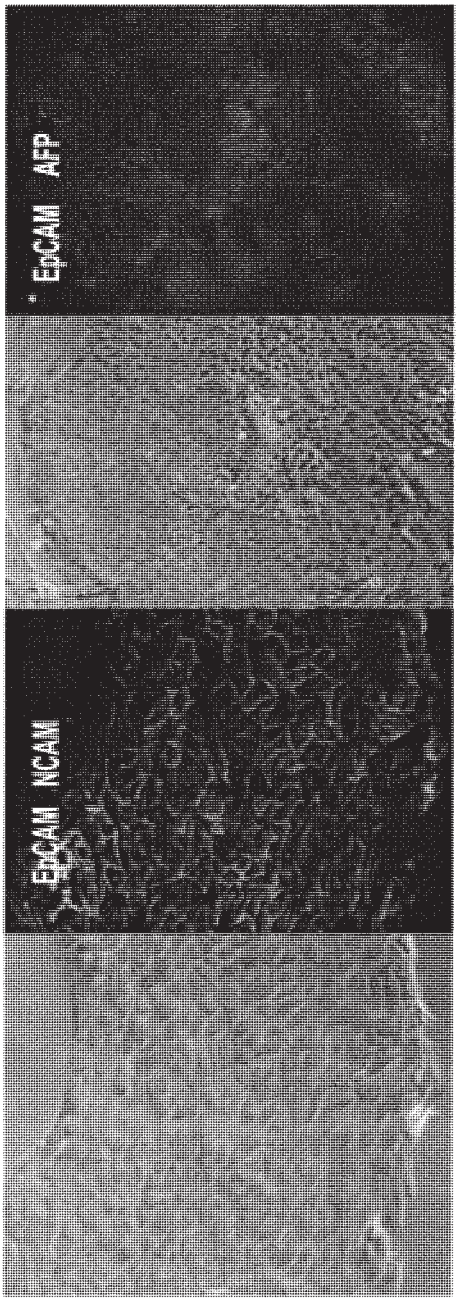


FIG. 11b

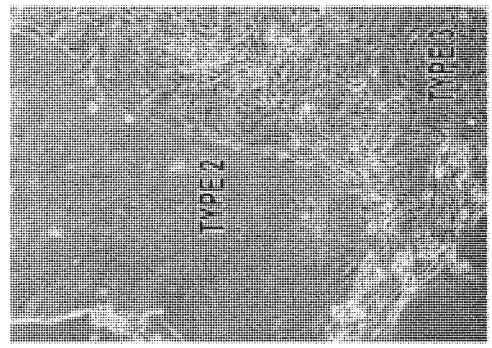


FIG. 11d



FIG. 11c

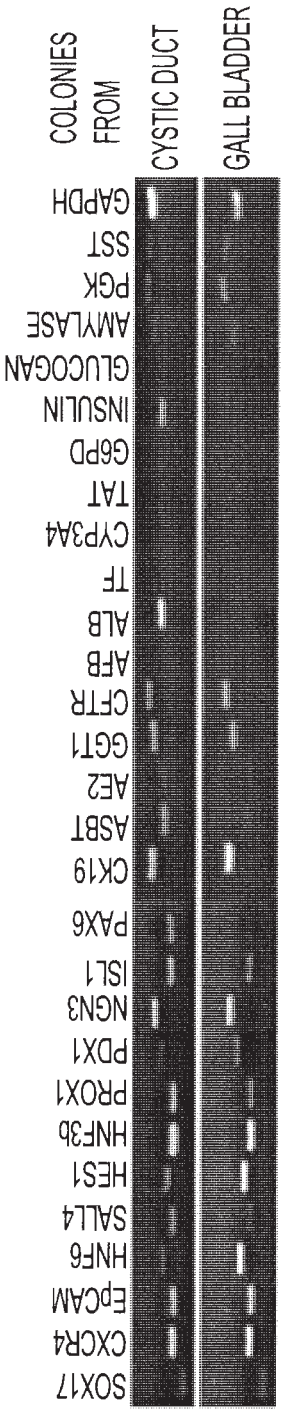


FIG. 11e

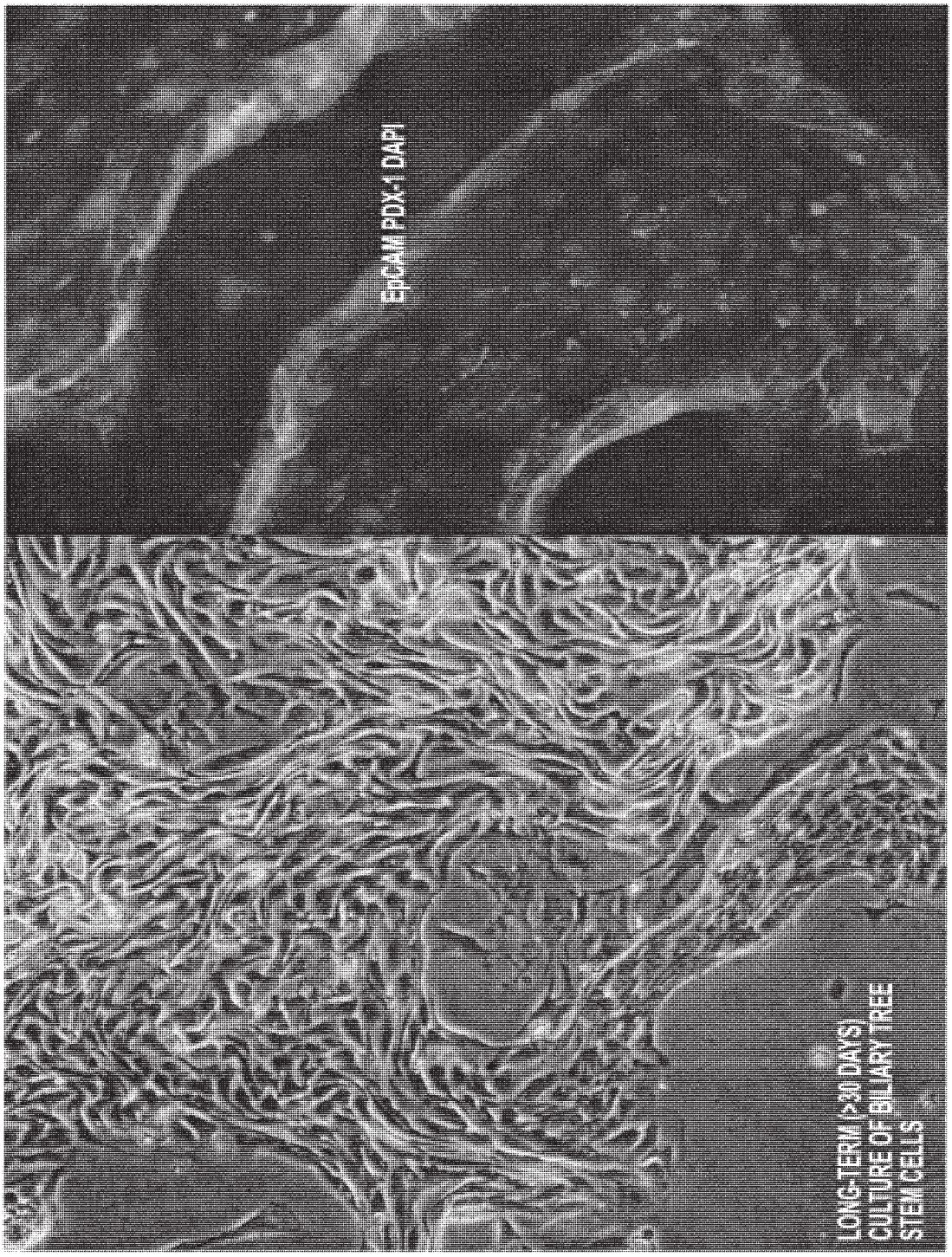

EpCAM PDX-1 DAPI
LONG-TERM (>30 DAYS)
CULTURE OF BILIARY TREE
STEM CELLS

FIG. 12

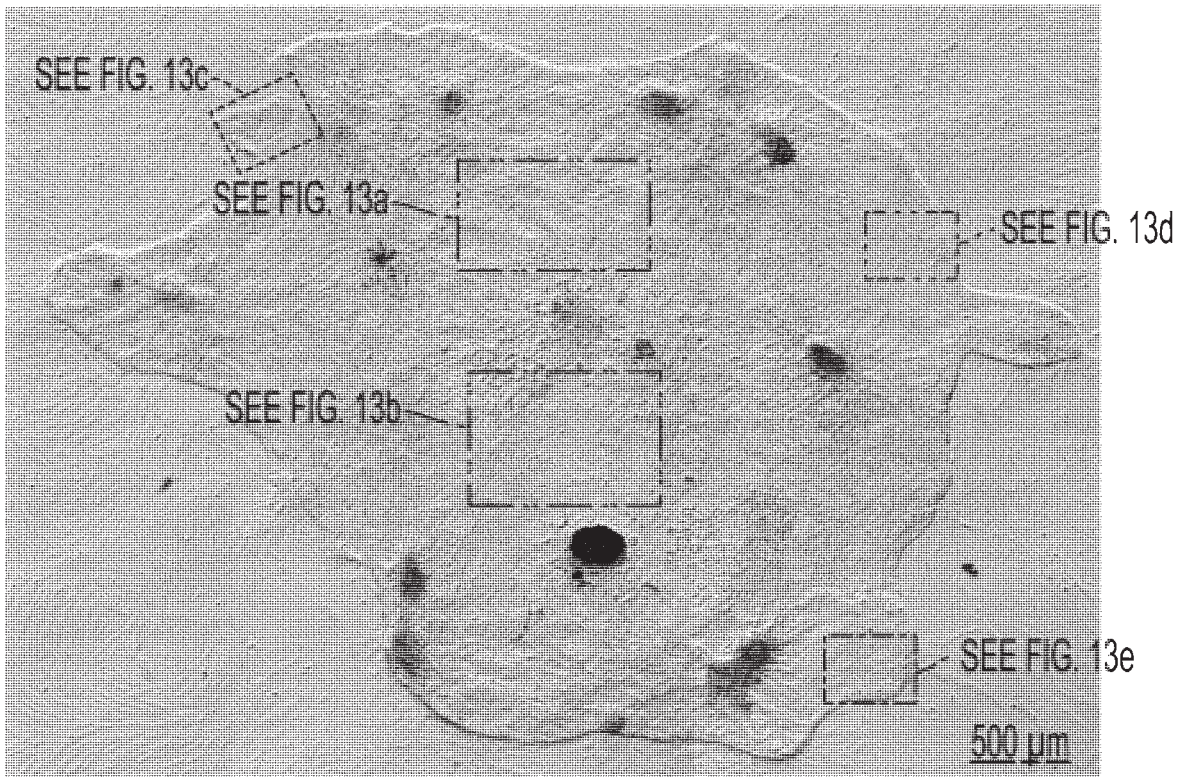


FIG. 13

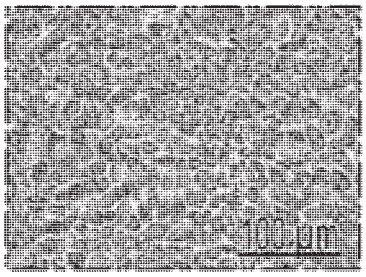


FIG. 13a

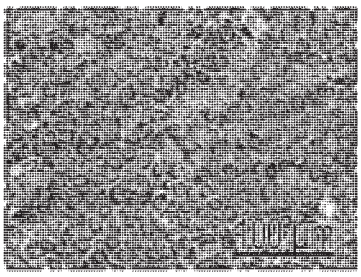


FIG. 13b

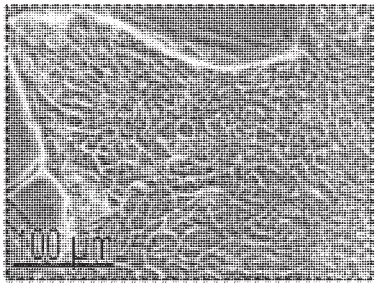


FIG. 13c

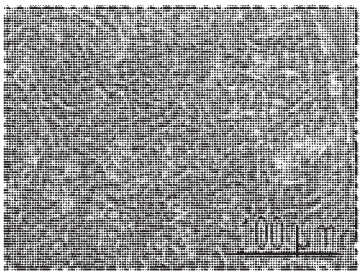


FIG. 13d

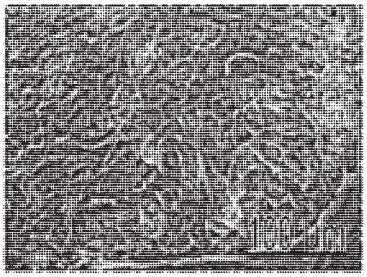


FIG. 13e

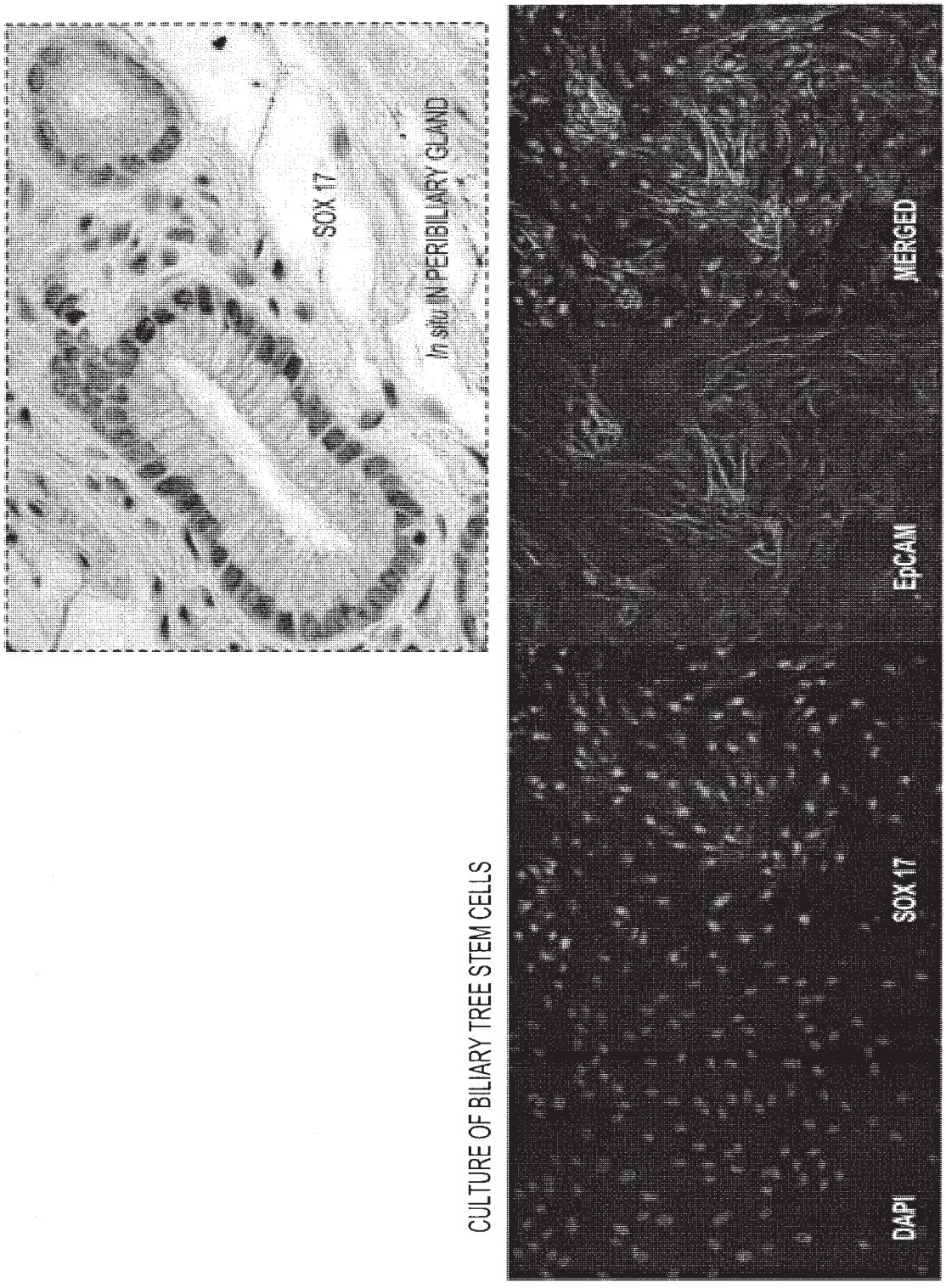

SOX 17
In situ IN PERIBILIARY GLAND
CULTURE OF BILIARY TREE STEM CELLS
DAPI
SOX 17
EpCAM
MERGED

FIG. 14

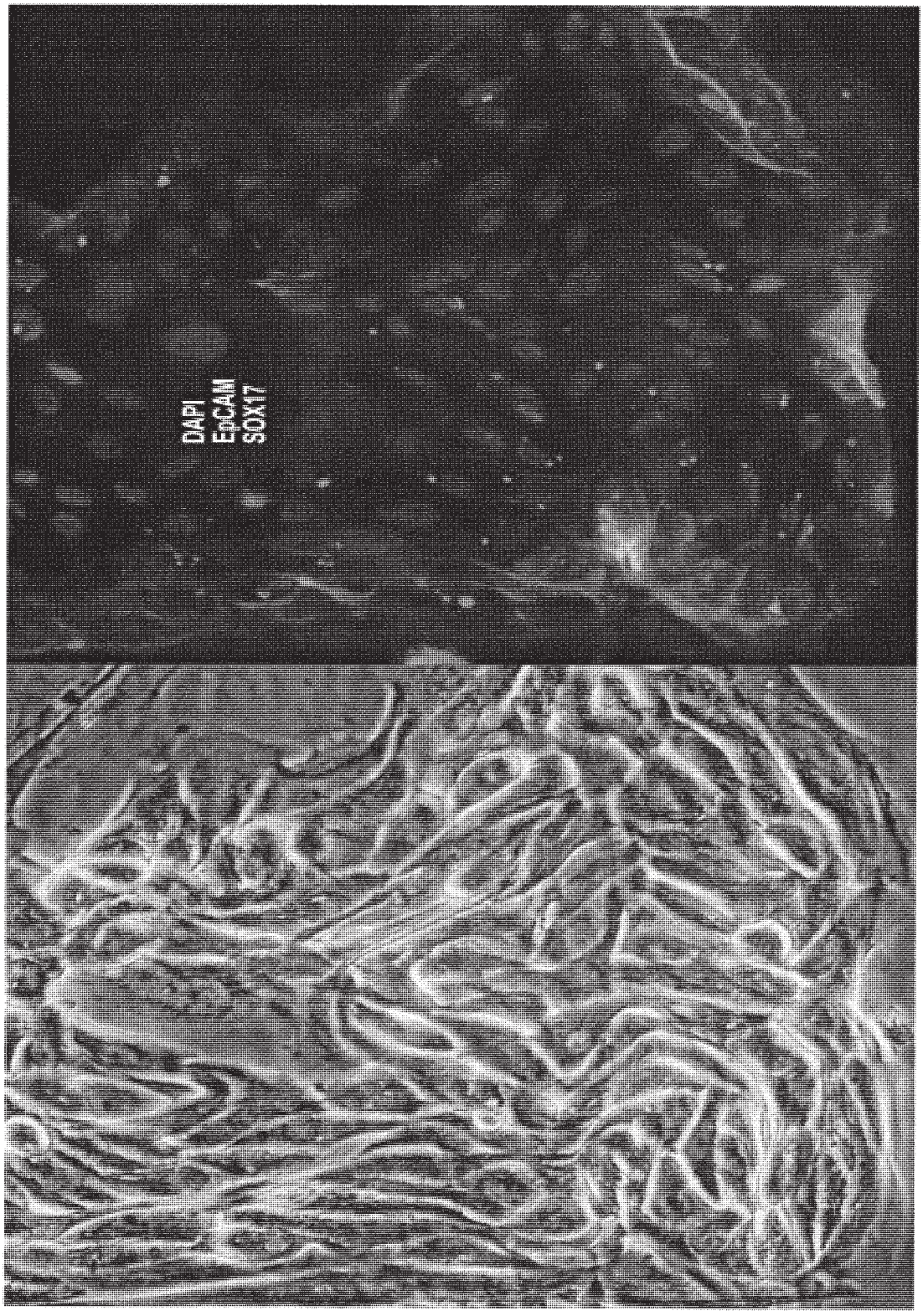


FIG. 15

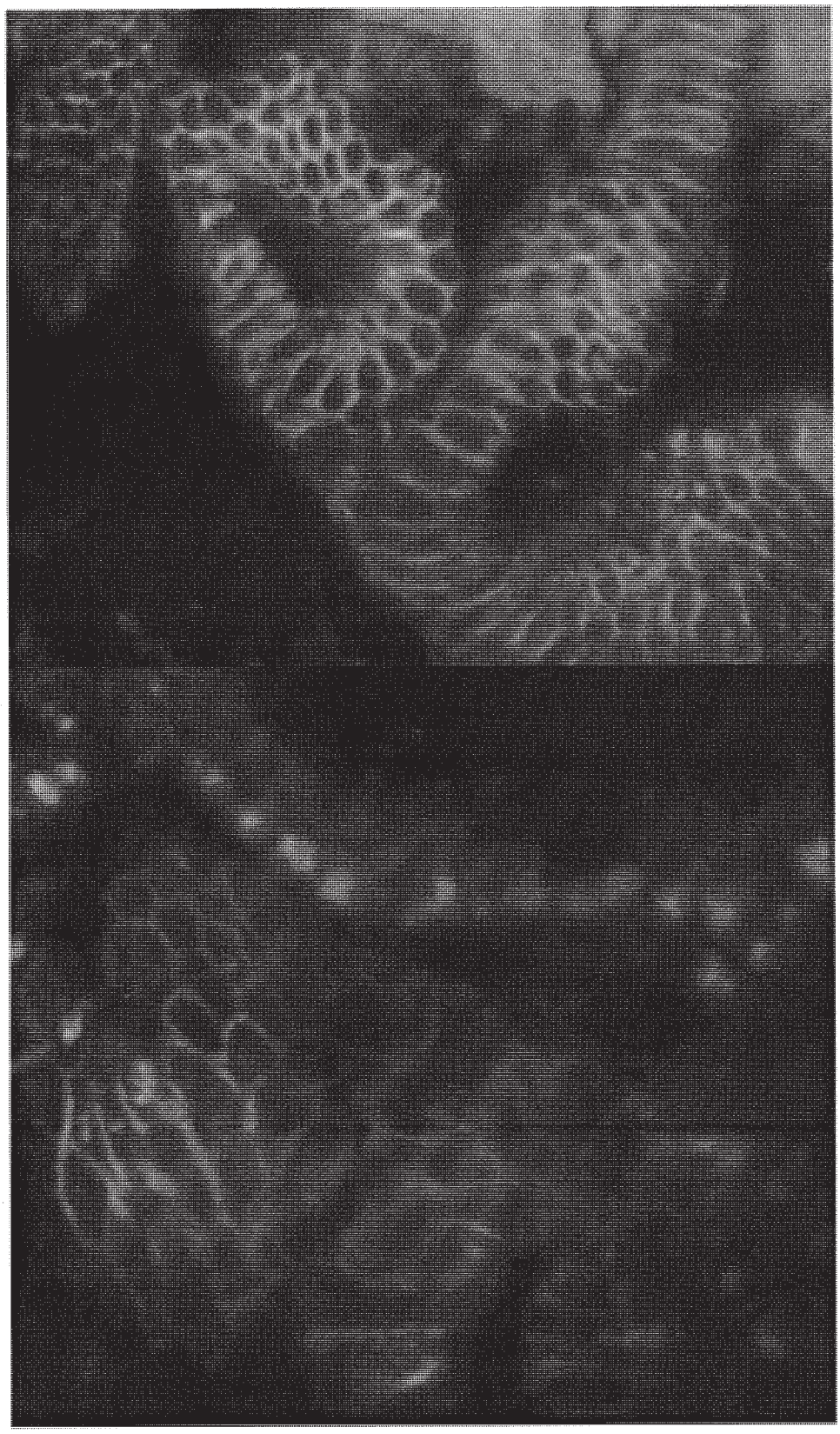


FIG. 16

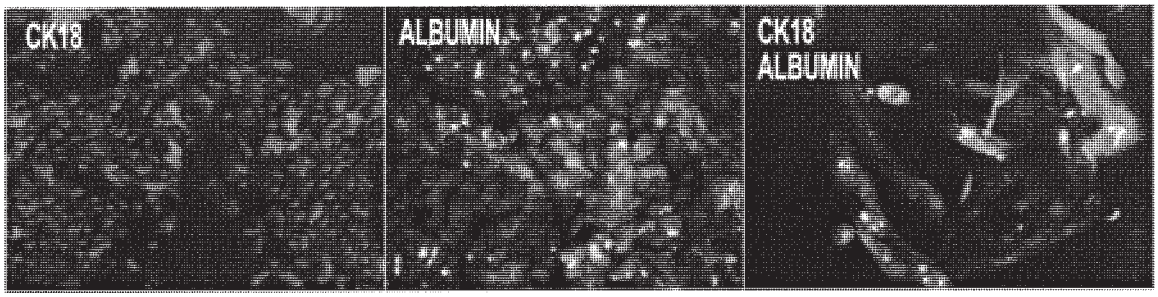


FIG. 17a

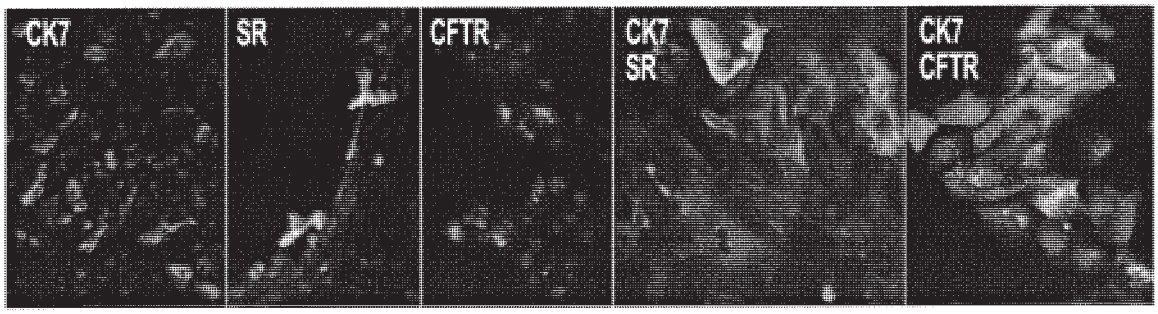


FIG. 17b

CONTROL CONDITION	SCORING: SEMI-QUANTITATIVE ESTIMATE OF CHOLANGIOCYTES OR HEPATOCYTES	
	SR+/CFTR+ CELLS	ALB+ /CK18+ CELLS
STEM CELL CONTROLS	0.2 ± 0.4	0
HDM CONTROLS	3 ± 0.7*	2.2 ± 0.8*

FIG. 17c

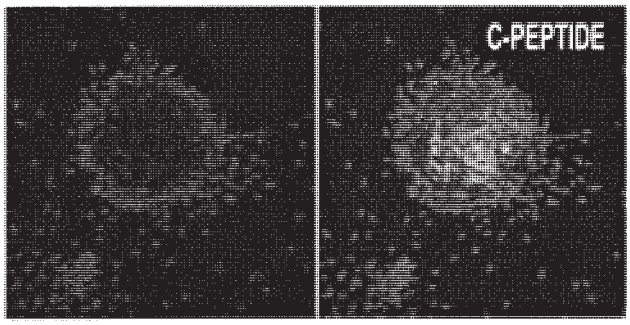


FIG. 18a

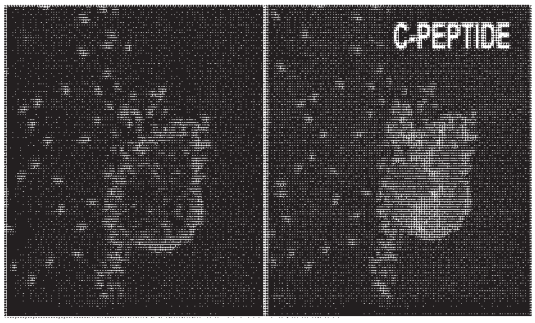


FIG. 18b

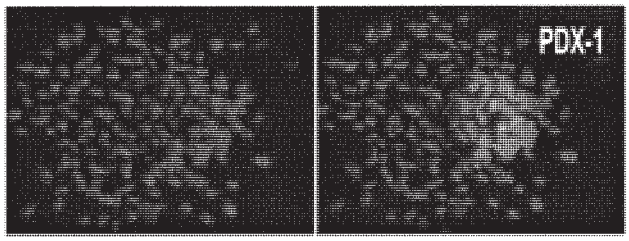


FIG. 18c

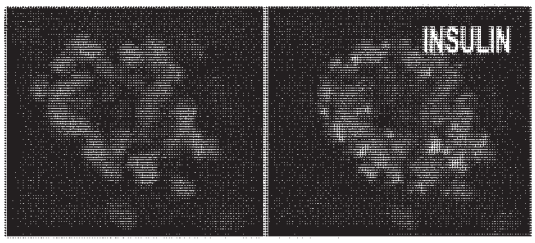


FIG. 18d

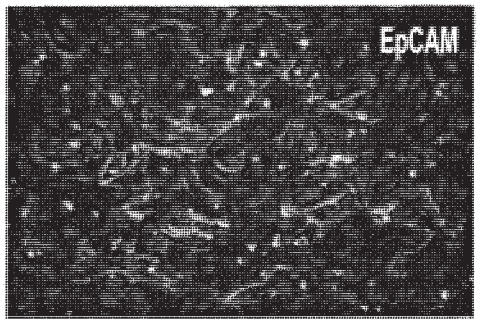


FIG. 18e

ISLET-LIKE STRUCTURES (c-pep+)	
STEM CELL CONTROLS	1 ± 0.7
HDM-P CONTROLS	3.8 ±1.3*

FIG. 18f

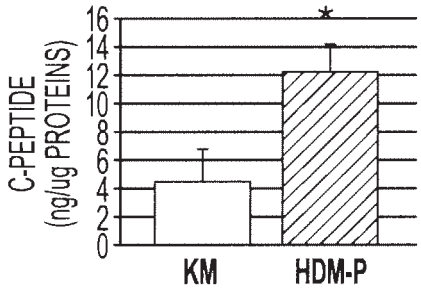


FIG. 18g

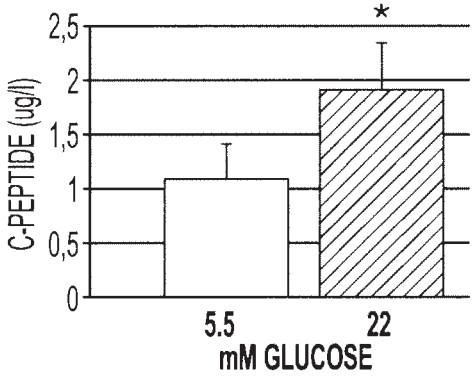
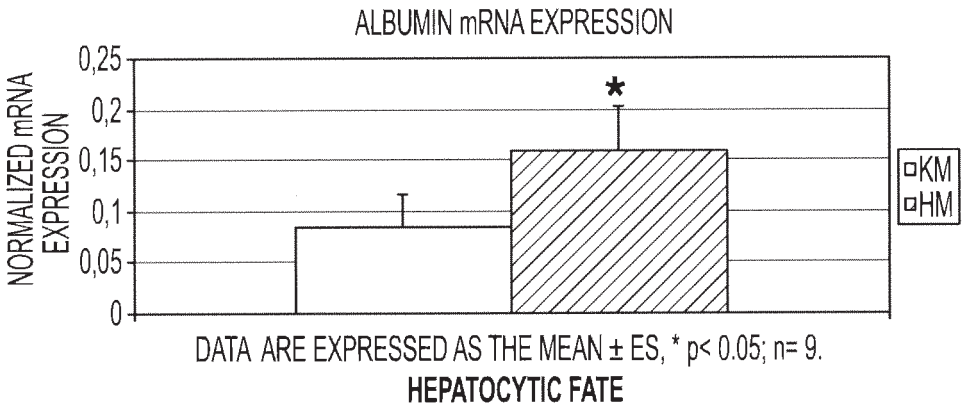
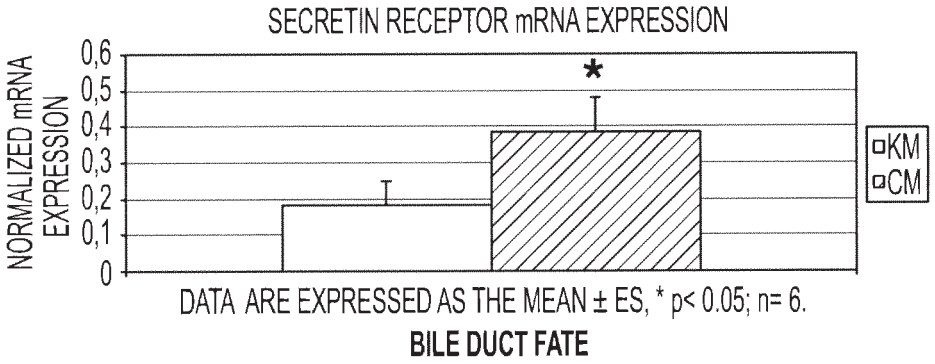


FIG. 18h


ALBUMIN mRNA EXPRESSION
NORMALIZED mRNA EXPRESSION
0,25
0,2
0,15
0,1
0,05
0
*
KM
HM
DATA ARE EXPRESSED AS THE MEAN ± ES, * p< 0.05; n= 9.
HEPATOCYTIC FATE


SECRETIN RECEPTOR mRNA EXPRESSION
NORMALIZED mRNA EXPRESSION
0,6
0,5
0,4
0,3
0,2
0,1
0
*
KM
CM
DATA ARE EXPRESSED AS THE MEAN ± ES, * p< 0.05; n= 6.
BILE DUCT FATE

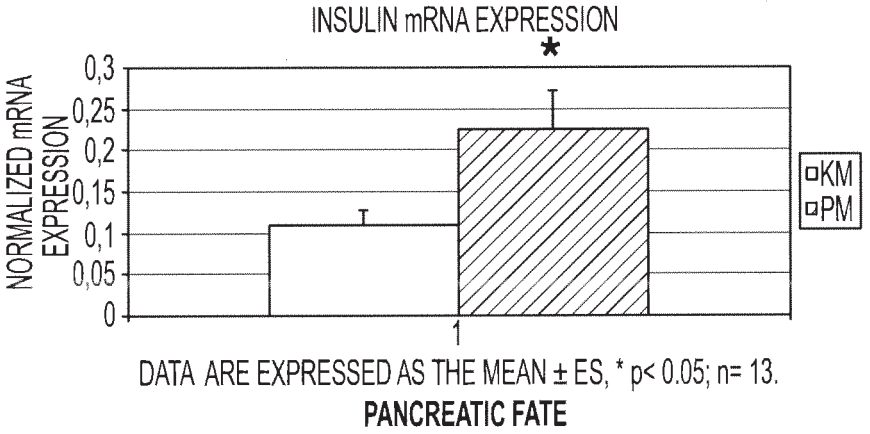

INSULIN mRNA EXPRESSION
NORMALIZED mRNA EXPRESSION
0,3
0,25
0,2
0,15
0,1
0,05
0
*
KM
PM
1
DATA ARE EXPRESSED AS THE MEAN ± ES, * p< 0.05; n= 13.
PANCREATIC FATE

FIG. 19



FIG. 20a

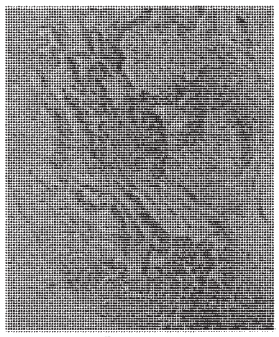


FIG. 20b

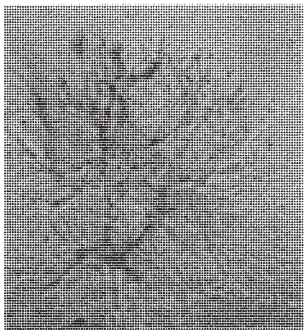


FIG. 20c

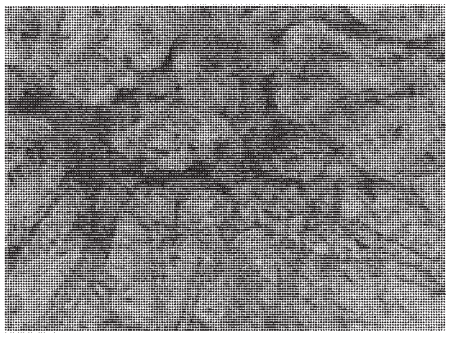


FIG. 20d

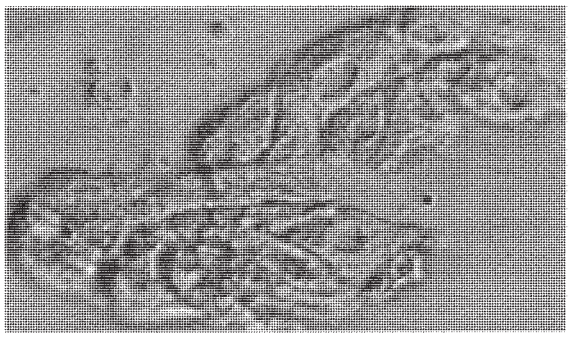


FIG. 20e

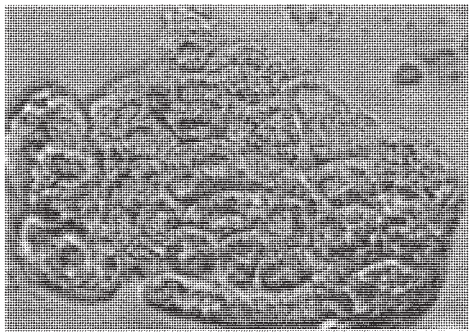


FIG. 20f

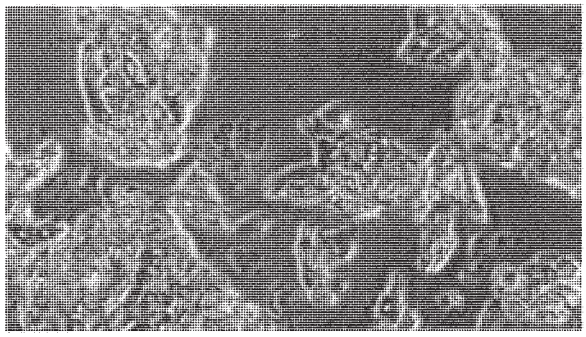


FIG. 20g

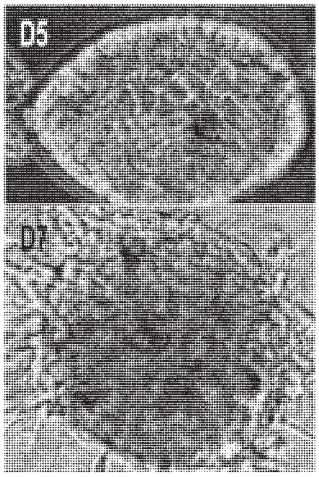


FIG. 20h

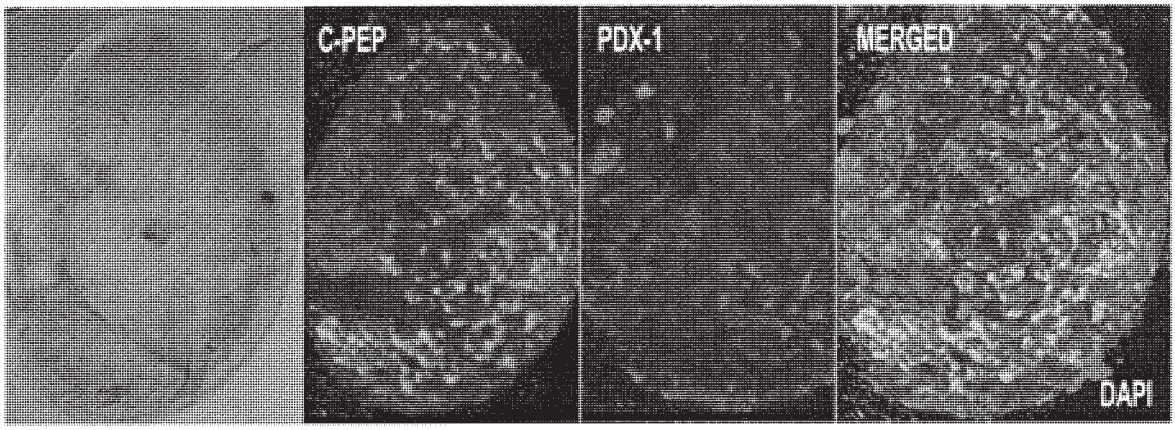


FIG. 20i

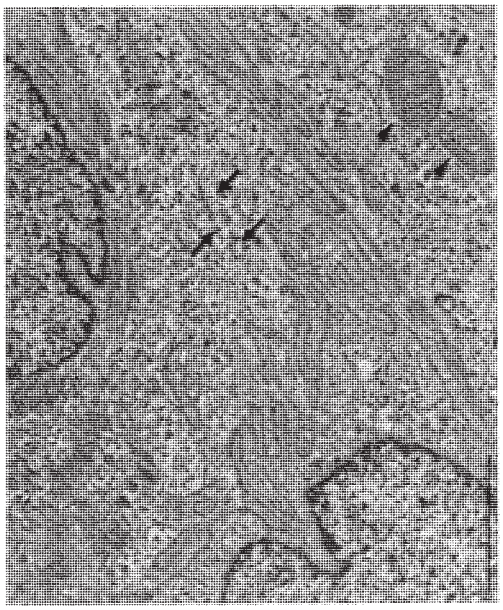


FIG. 21b

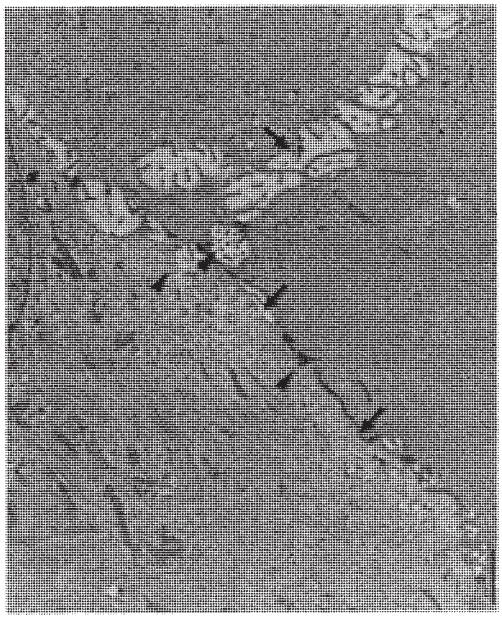


FIG. 21d

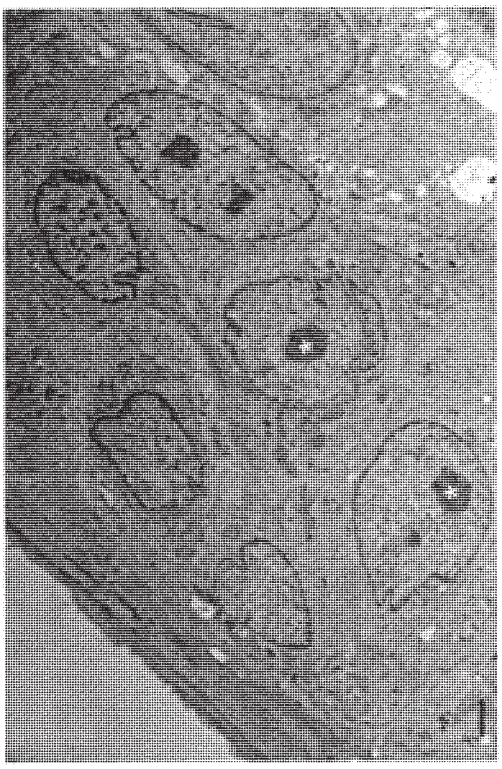


FIG. 21a



FIG. 21c

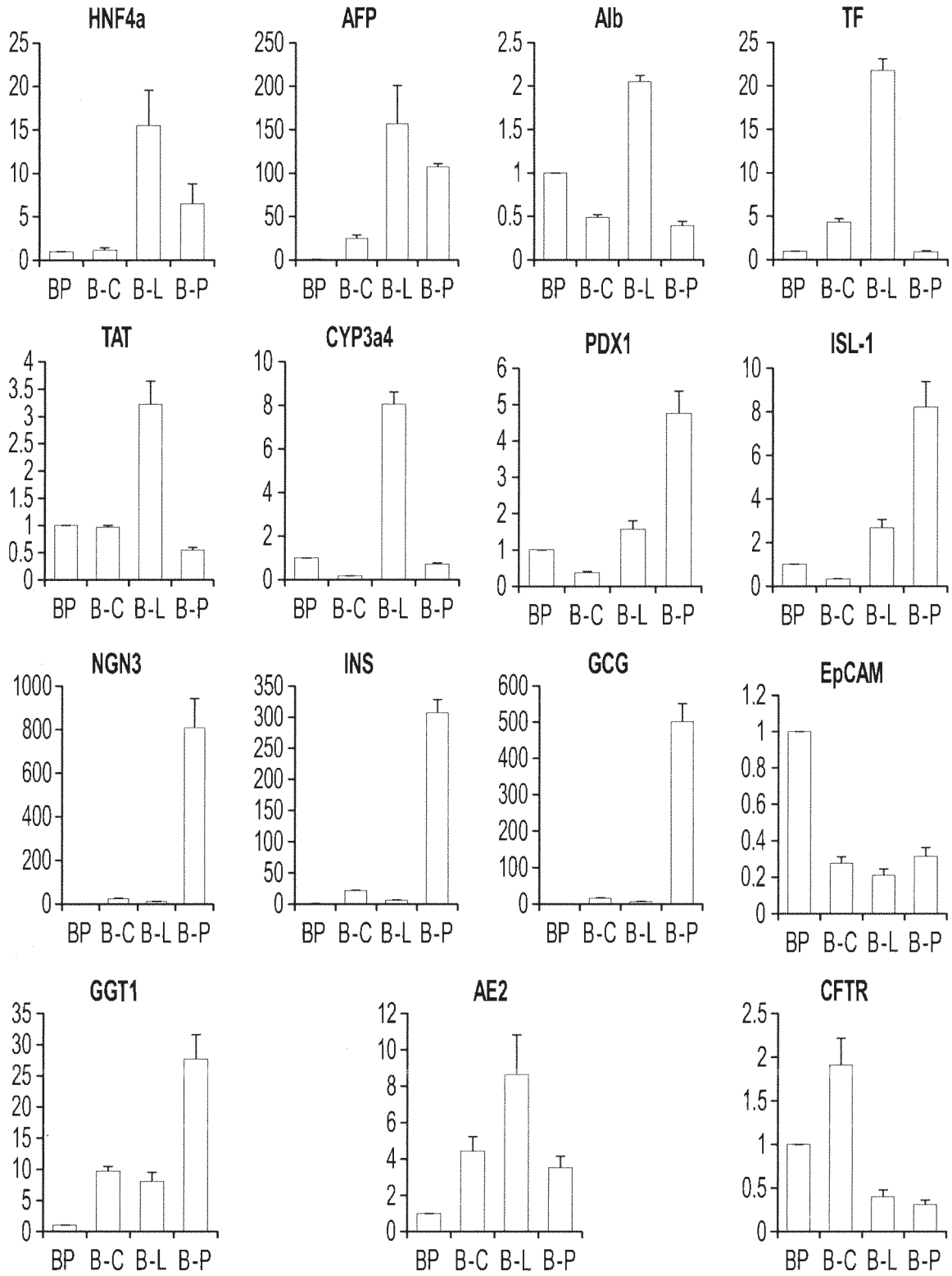

HNF4a
AFP
Alb
TF
TAT
CYP3a4
PDX1
ISL-1
NGN3
INS
GCG
EpCAM
GGT1
AE2
CFTR
BP B-C B-L B-P

FIG. 22

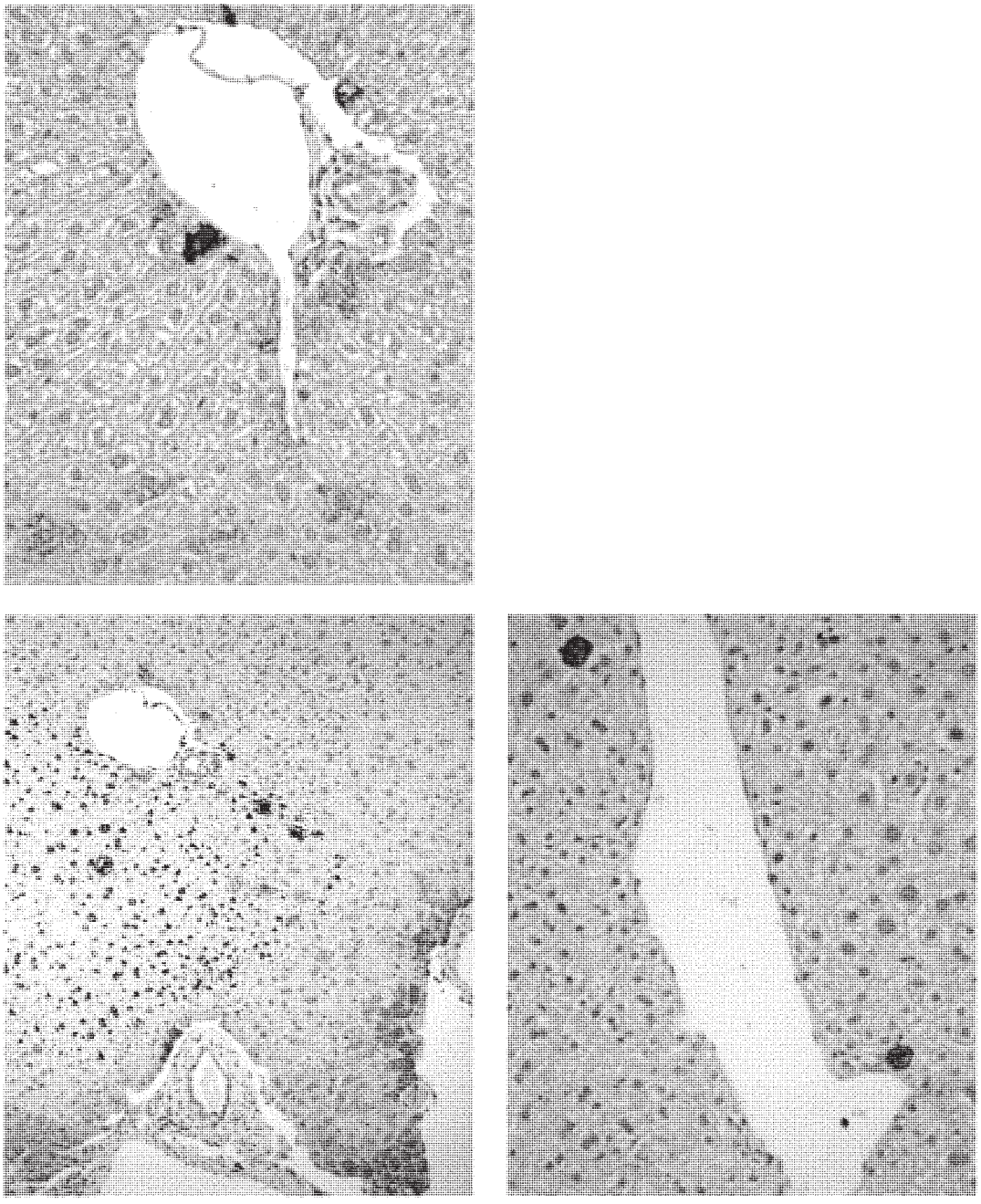


FIG. 23

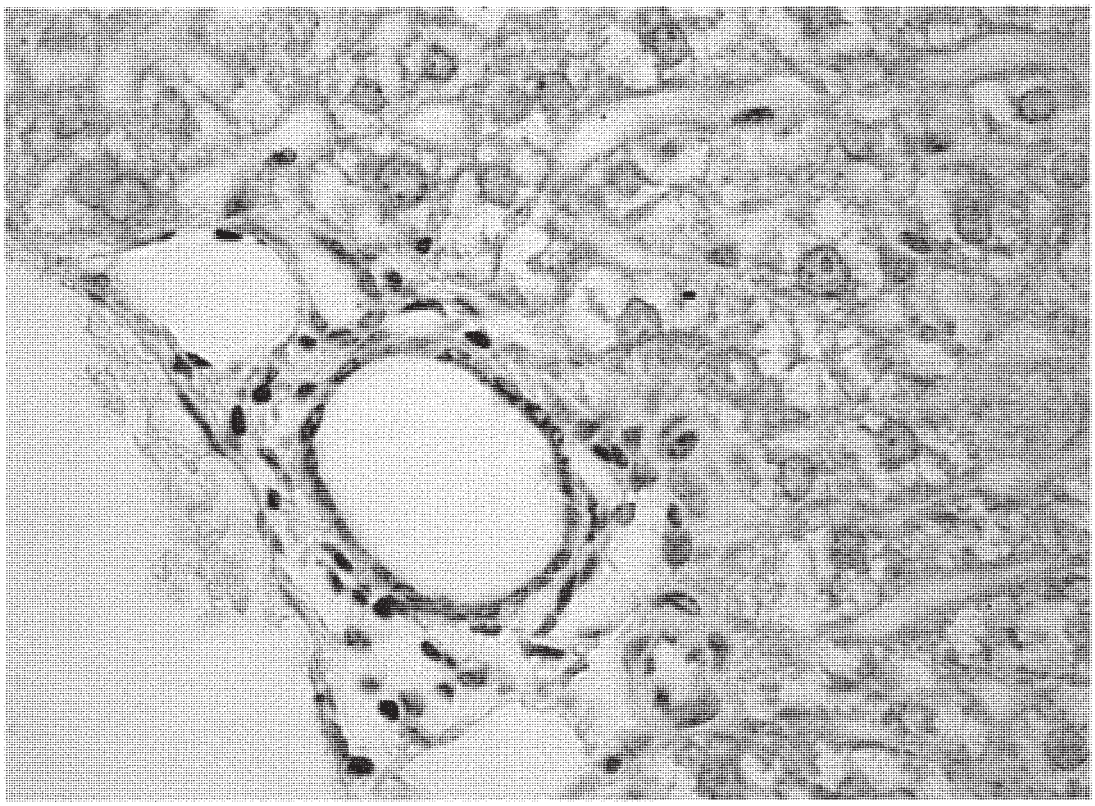


FIG. 24

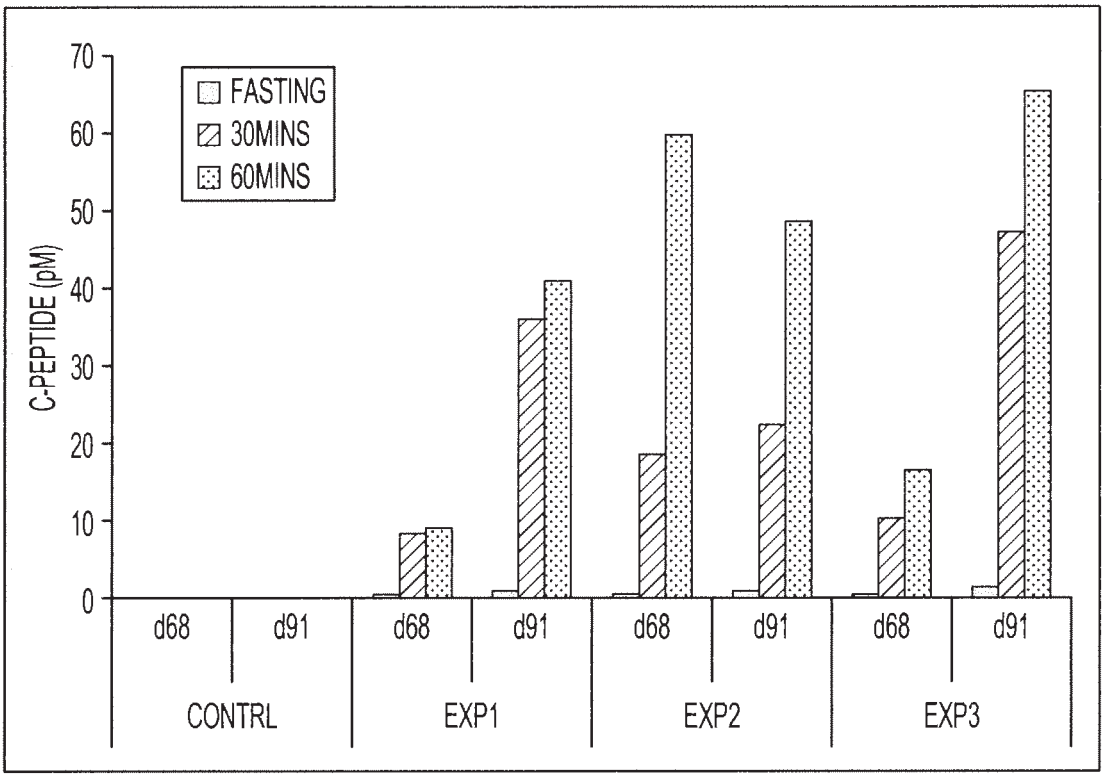

70
60
50
40
30
20
10
0
C-PEPTIDE (pM)
FASTING
30MINS
60MINS
d68
d91
d68
d91
d68
d91
d68
d91
CONTRL
EXP1
EXP2
EXP3

FIG. 25