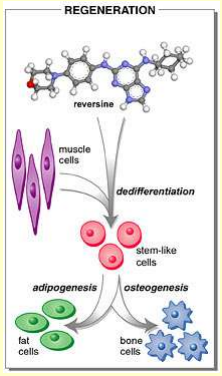
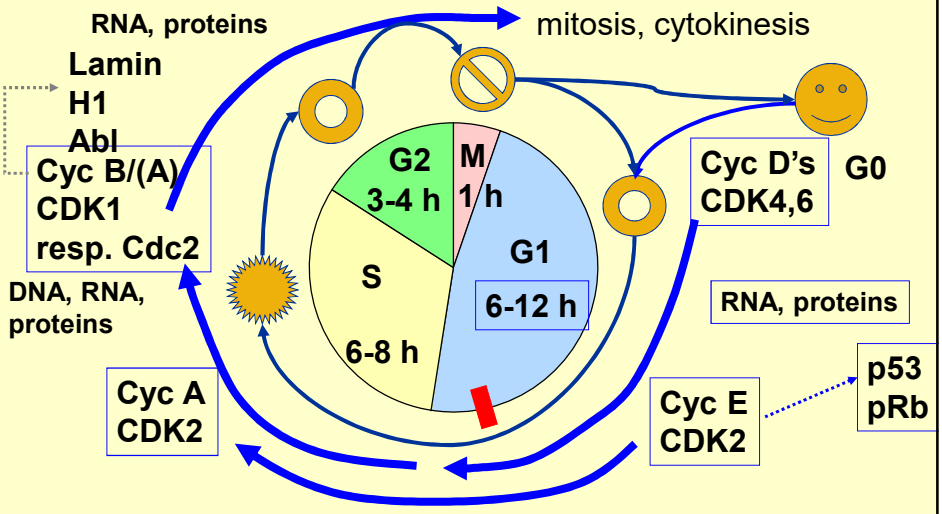
Dedifferentiation



Cell cycle

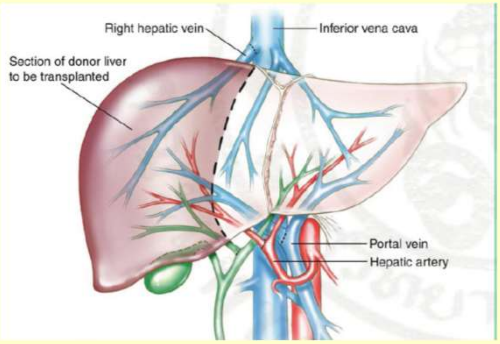


Dedifferentiation

- loosing of specific features

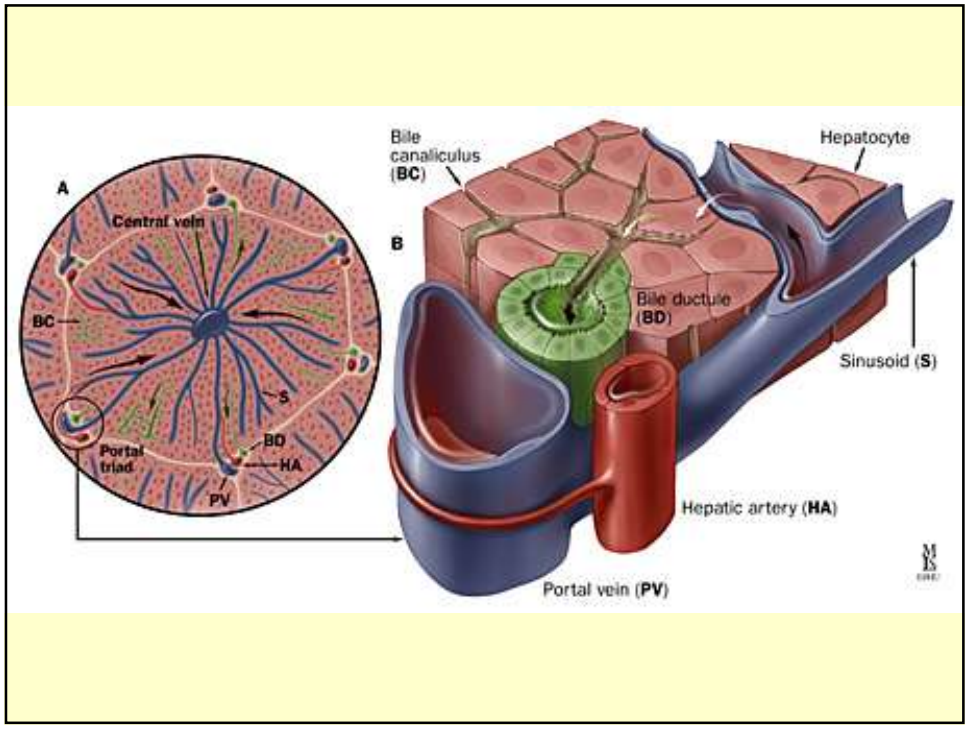
- return into cell cycle

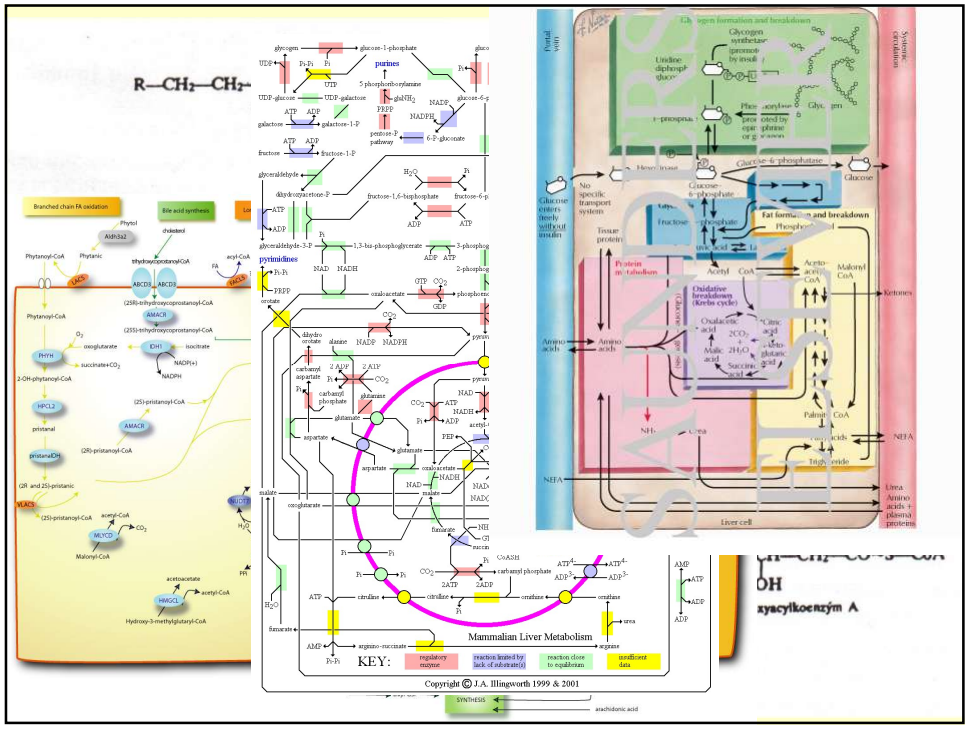
- it is often possible to see under *in vitro* conditions
- it is possible to see during culturing of immortalized cell lines
- cell are loosing specific features that make them distinct from stem cells or other differentiated cells
- changes can be induced by absence of appropriate stimuli from the environment
- changes in gene expression
- synthesis of new proteins
- cell can not perform functions conditioned by differentiation
- usually dedifferentiation is accompanied by changes in cell morphology



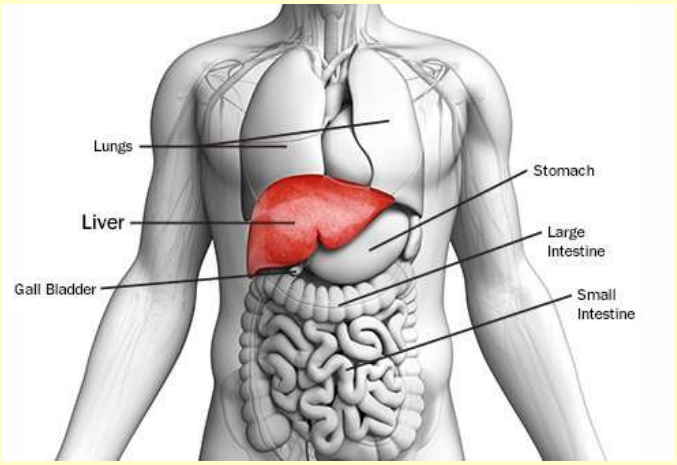
Liver – *hepar* is the biggest gland in the human body. Its weight is circa 1500 g in human.

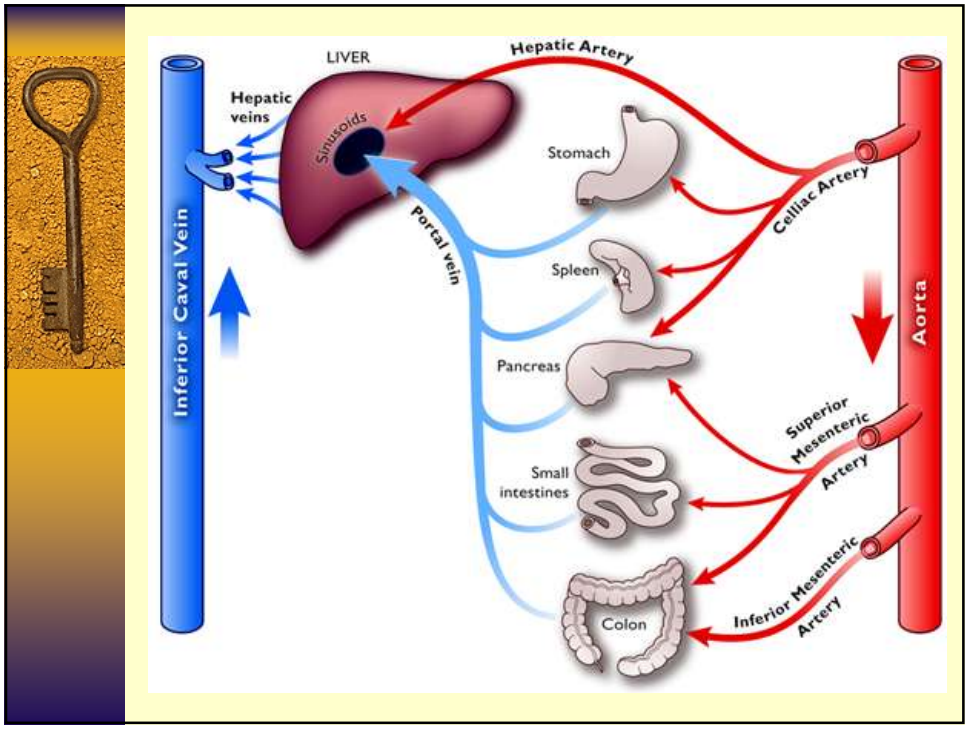
The mammals have big liver with several lobes. It is possible to perform biopsy and cultivate cells under in vitro conditions. Liver's dual blood supply. The portal vein provides about two thirds of the blood. This blood contains oxygen and many nutrients brought to the liver from the intestines for processing. The hepatic artery provides the remaining one third of blood. This oxygen-rich blood comes from the heart and provides the liver with about half of its oxygen supply.


A
Central vein
BC
S
BD
HA
PV
Portal triad
B
Bile canaliculus (BC)
Hepatocyte
Bile ductule (BD)
Sinusoid (S)
Hepatic artery (HA)
Portal vein (PV)

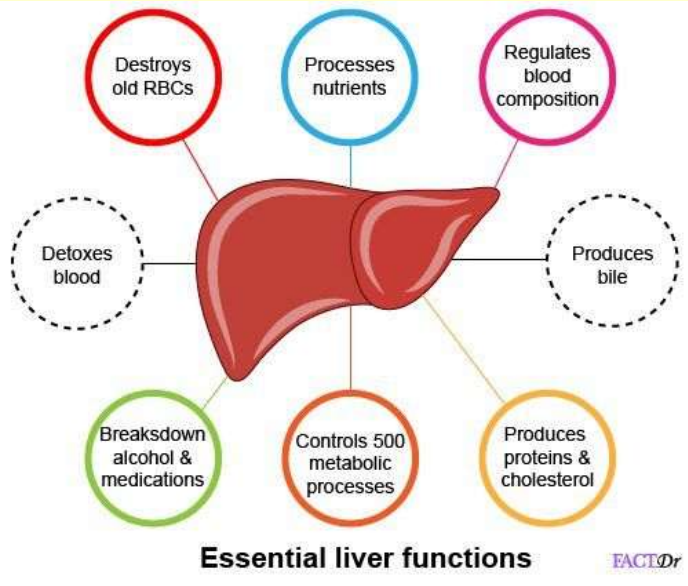

R—CH₂—CH₂—
Mammalian Liver Metabolism
KEY:
Copyright © J.A. Illingworth 1999 & 2001
xyacylkoenzým A

- protein metabolism
- lipid metabolism
- polysaccharides metabolism
- hem synthesis
- bilirubin metabolism
- bile acid metabolism
- urea cycle cycle
- drug metabolism
- hepatotoxicity





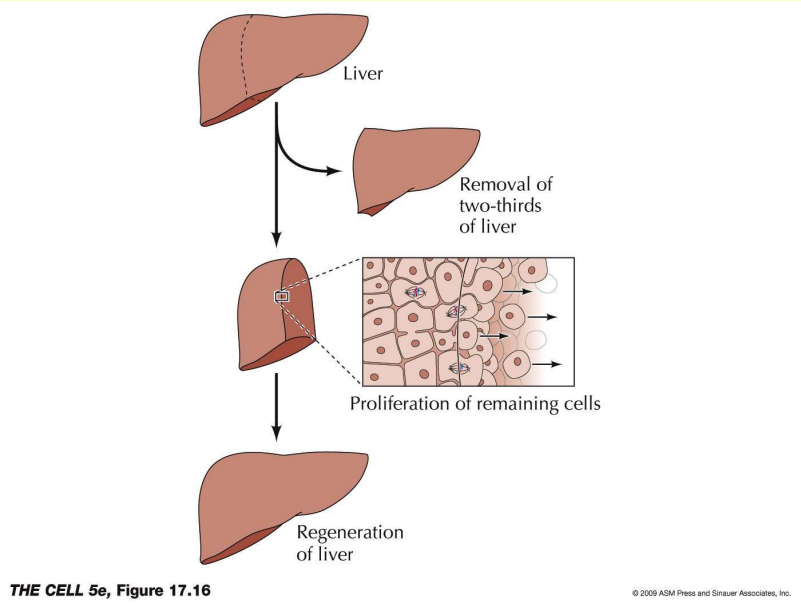
Liver functions



Stem cells and tissue regeneration in adult individuals

Liver cells usually stay in G0 phase of cell cycle and can be stimulated to proliferate if there is a huge decrease in liver cell number.

Liver regeneration



THE CELL 5e, Figure 17.16

© 2009 ASM Press and Sinauer Associates, Inc.

Partial hepatectomy

- partial hepatectomy with resection of 2/3 of rat liver
- residual tissue can enlarge to renew previous capacity

1. completely resected lobes can growth again
2. process lasts cca. 5-7 days

- used as an experimental set up because:
  - there is no inflammation or tissue damage
  - particular stimulus initiating regeneration is not exactly identified

Partial hepatectomy

- regeneration is proportional to resected tissue
- if resection is small (<10%) regeneration cen be complete

Volume of liver tissue is precisely regulated

- When big dog is donor for transplantation for small dog, volume of liver tissue decreases unless it is proportional to small dog body weight.
- Xenotransplantation
- In two cases liver of baboon transplanted to human increased volume to achieve size proportional to human body size.

What is activated after PHx?

- Epithel regeneration depends on presence of small number of progenitor or stem cells.
- Proliferation of all cells is induced after PHx in liver

What do influence hepatocyte proliferation?

- start of DNA synthesis afate HPx influences

1. LD cycle
2. food intake
3. and others

How long does it take until new DNA is synthesized?

- 10 -12 hours in rat
  - it depends on animal species
- The first peak in hepatocyte proliferation occurs in 24h, another one after 36 - 48 hours.

How many cell cycles are needed to acheive original liver size?

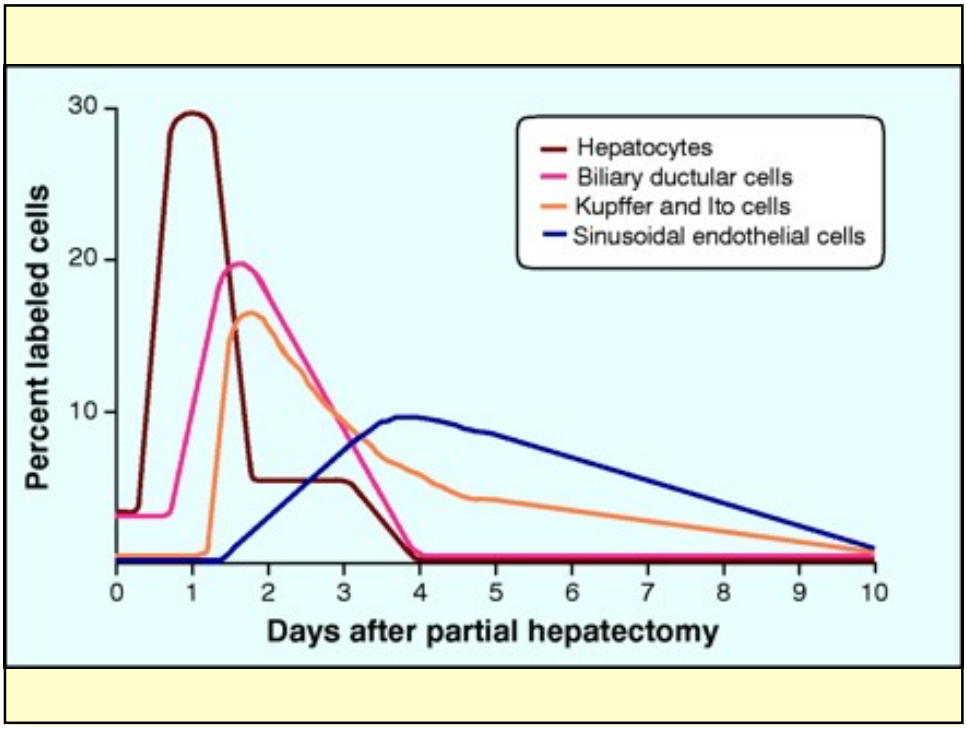
- 2/3 liver tissue is resected

→1.66 cell cycles are needed per one hepatocyte

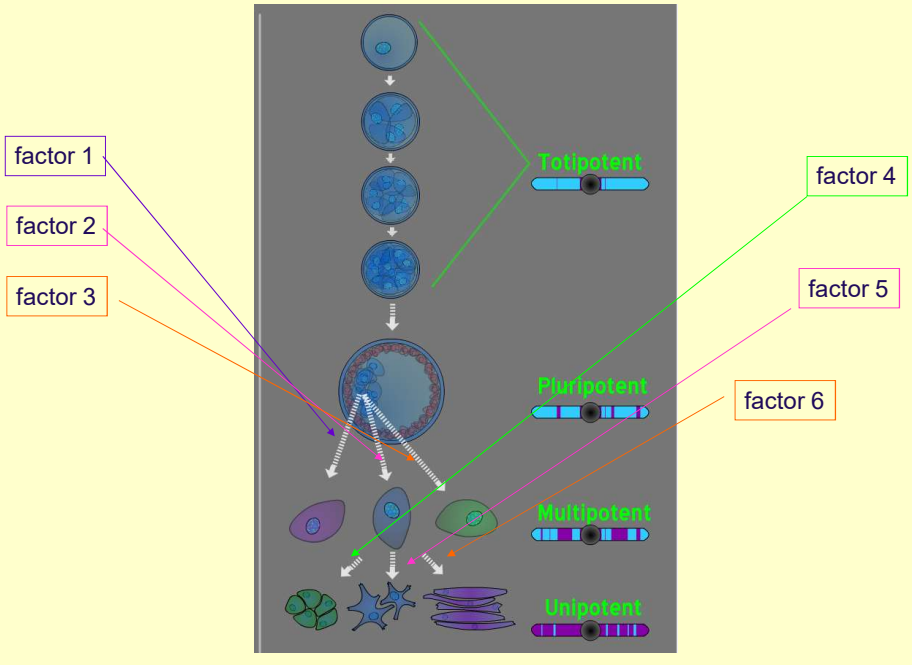
→The most of hepatocytes (95% in young and 75% in old rats) overcome one or two proliferative cycles.

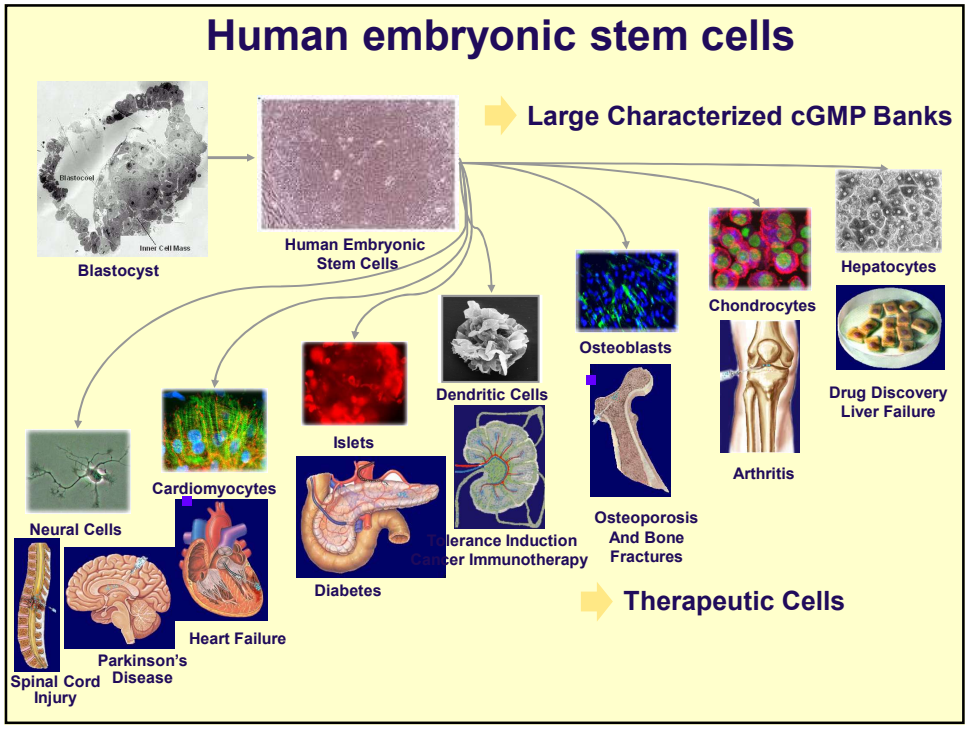
What happens after hepatocyte proliferation?

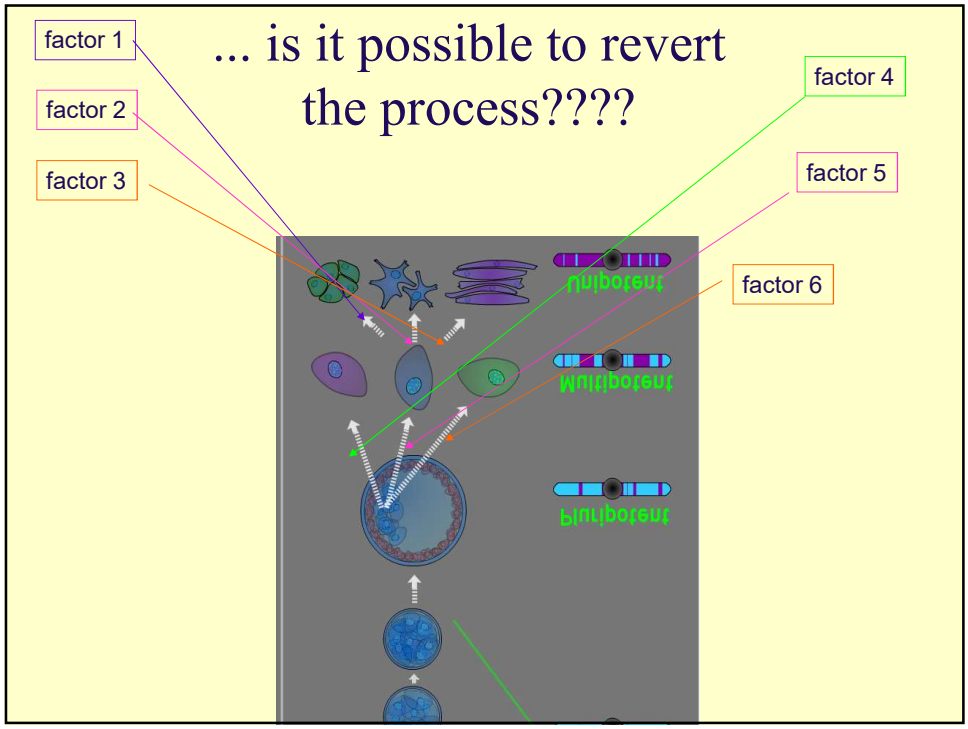
- hepatocytes produce mitogenic stimuli that initiate proliferation of other liver cells
  - kinetics of cell proliferation
  - growth factors produced by proliferating hepatocytes
  - after 2 - 3 days all cell types in the liver are proliferating
- on day 3 - 4 – liver histology shows clusters of small hepatocytes surrounding capillaries.



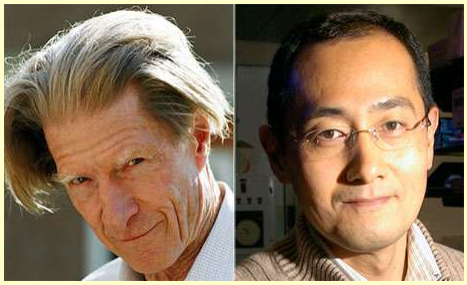
Differentiation - principle



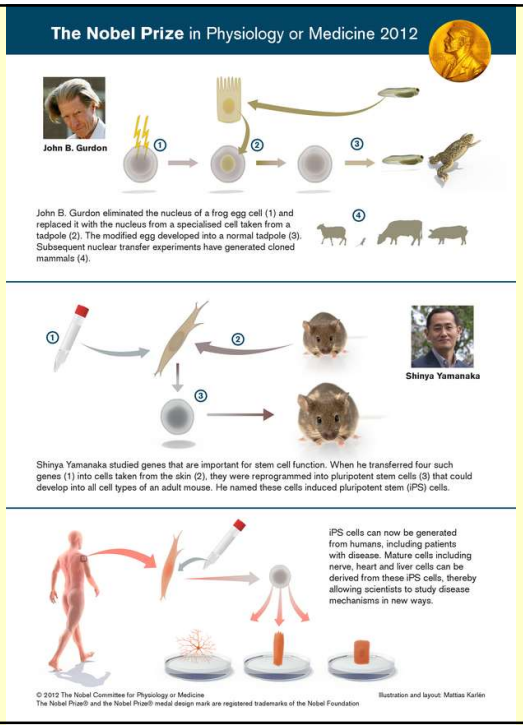

Human embryonic stem cells
Large Characterized cGMP Banks
Blastocyst
Human Embryonic Stem Cells
Hepatocytes
Chondrocytes
Osteoblasts
Drug Discovery Liver Failure
Dendritic Cells
Islets
Cardiomyocytes
Neural Cells
Arthritis
Osteoporosis And Bone Fractures
Tolerance Induction Cancer Immunotherapy
Diabetes
Heart Failure
Parkinson's Disease
Spinal Cord Injury
Therapeutic Cells


... is it possible to revert the process????
factor 1
factor 2
factor 3
factor 4
factor 5
factor 6
Unipotent
Multipotent
Pluripotent

Stem Cell Discoveries Win Nobel Prize 2012

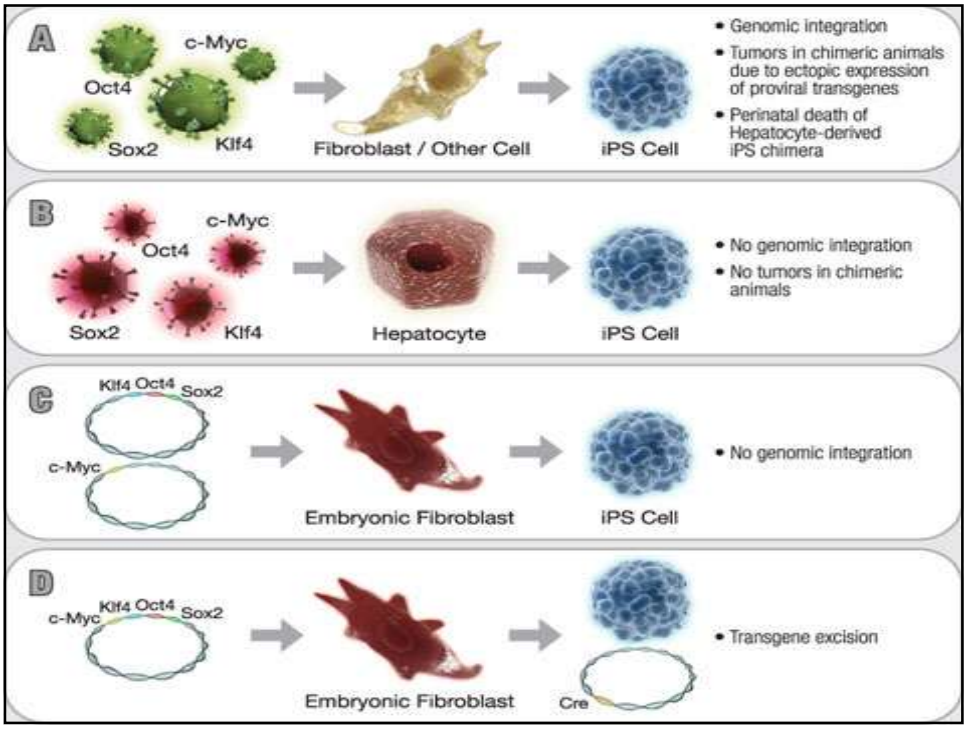


John B. Gurdon of the University of Cambridge & Shinya Yamanaka of Kyoto University the Nobel Prize in Medicine



1962

http://www.leica-microsystems.com/science-lab/nobel-prize-2012-in-physiology-or-medicine-for-stem-cell-research/



thank you for your attention