Glivec enhances the stem cell mediated liver regeneration

Peter Nagy

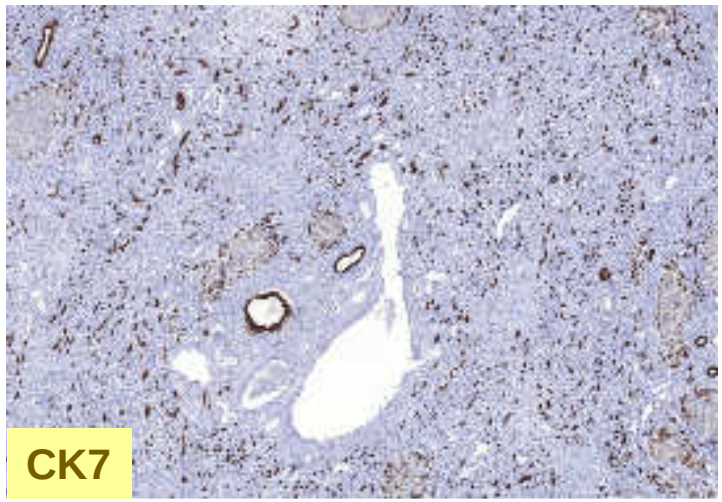
Semmelweis University, Ist Dept of Pathology and Experimental Cancer Research

Glivec (imatinib mesylate)

- Tyrosine kinase inhibitor (bcr-abl, c-kit, PDGFR)
- Clinical applications : CML, GIST, ALL etc.
- Non oncological applications: fibromatoses, primary pulmonary hypertension, liver fibrosis

Ductular reaction

- It is present in almost all forms of chronic hepatic injury
- It may derive from progenitor/stem cells
- It may contribute to liver regeneration
- It is closely related with myofibroblasts
- Stem cell factor and PDGF are thought to be important regulators

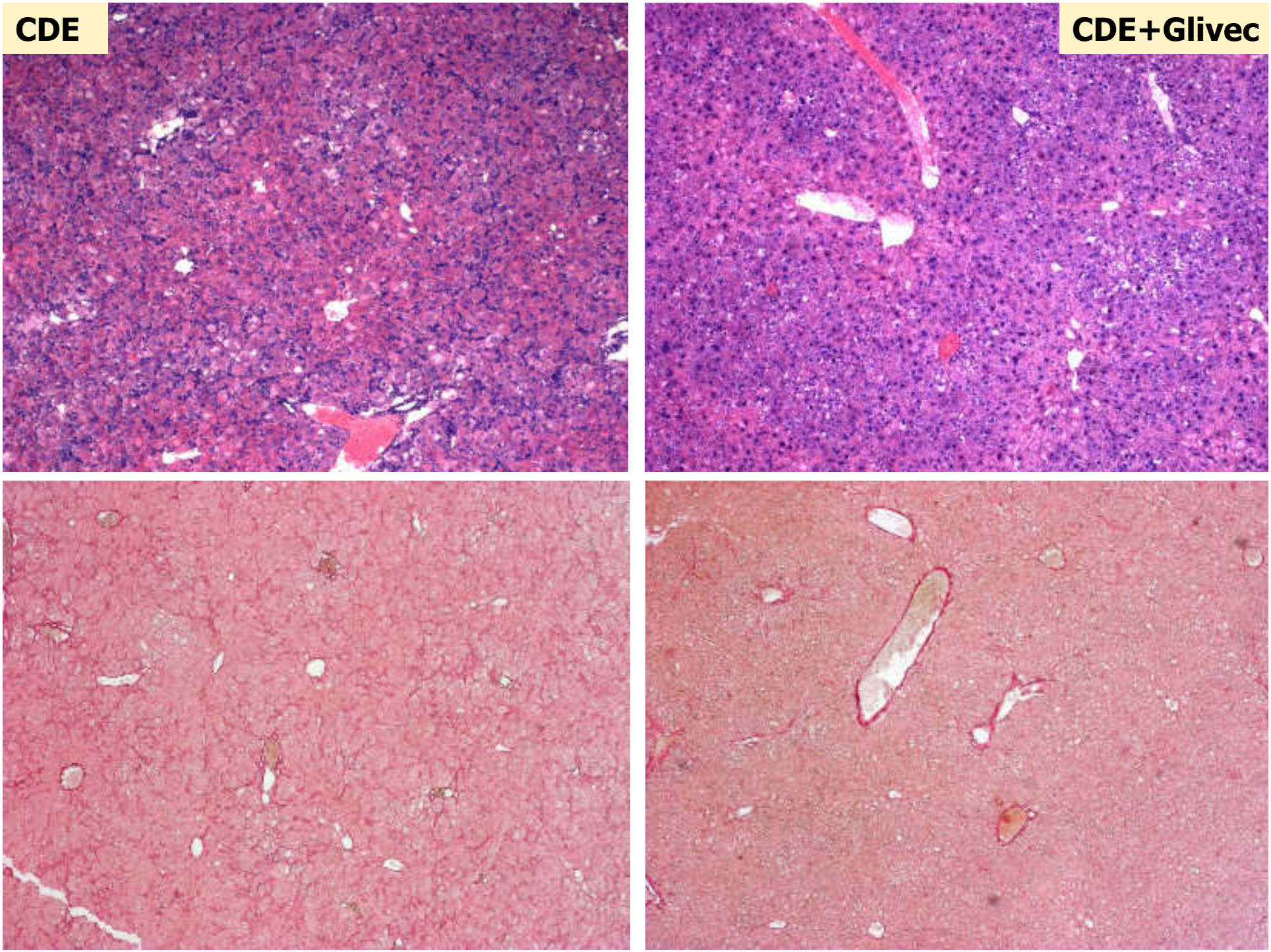


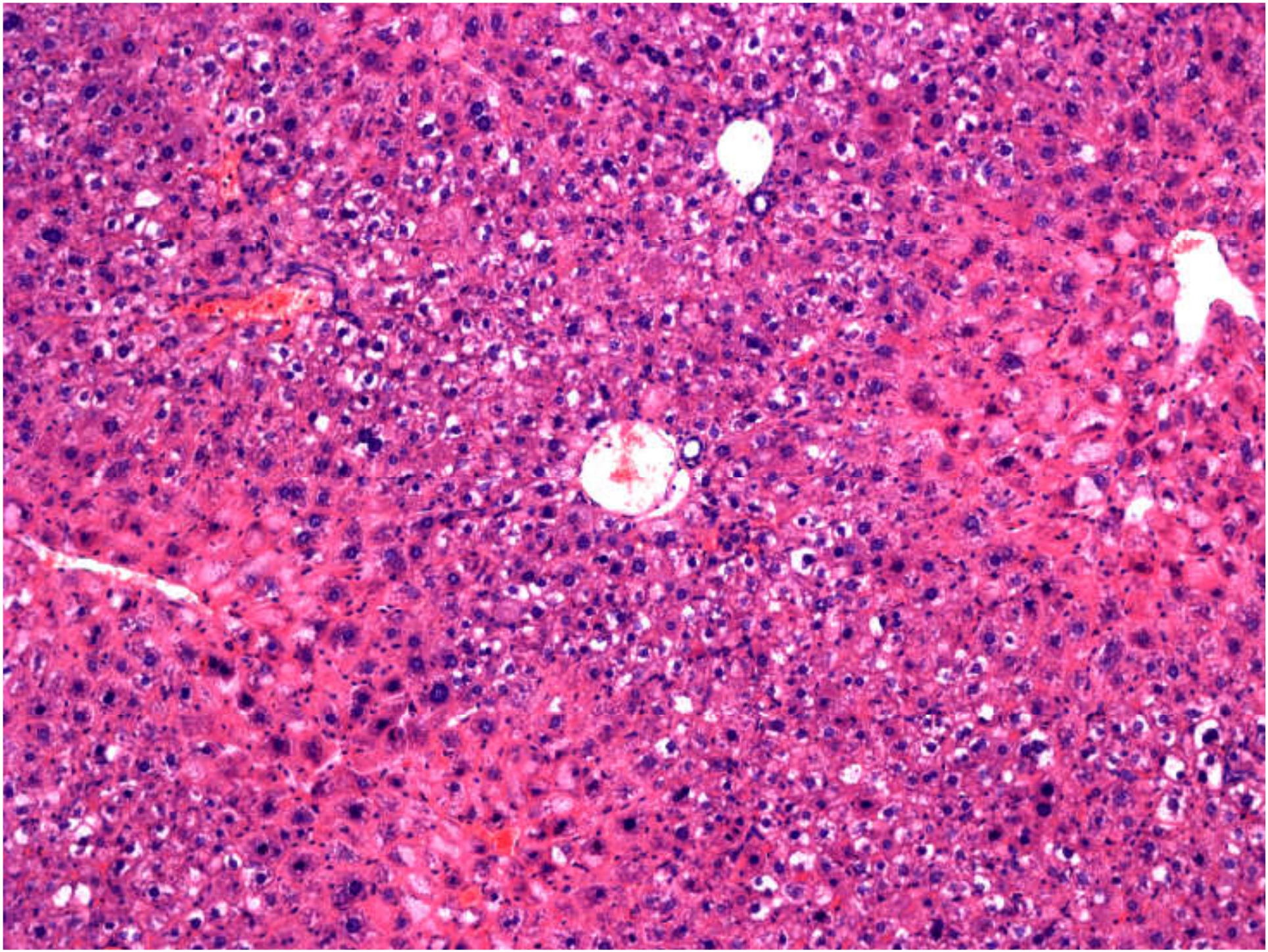
Glivec and liver

- Ductular reactions are frequently associated with liver fibrosis
- PDGFR is expressed by hepatic myofibroblasts
- Glivec succesfully decreased liver fibrosis in several experimental models

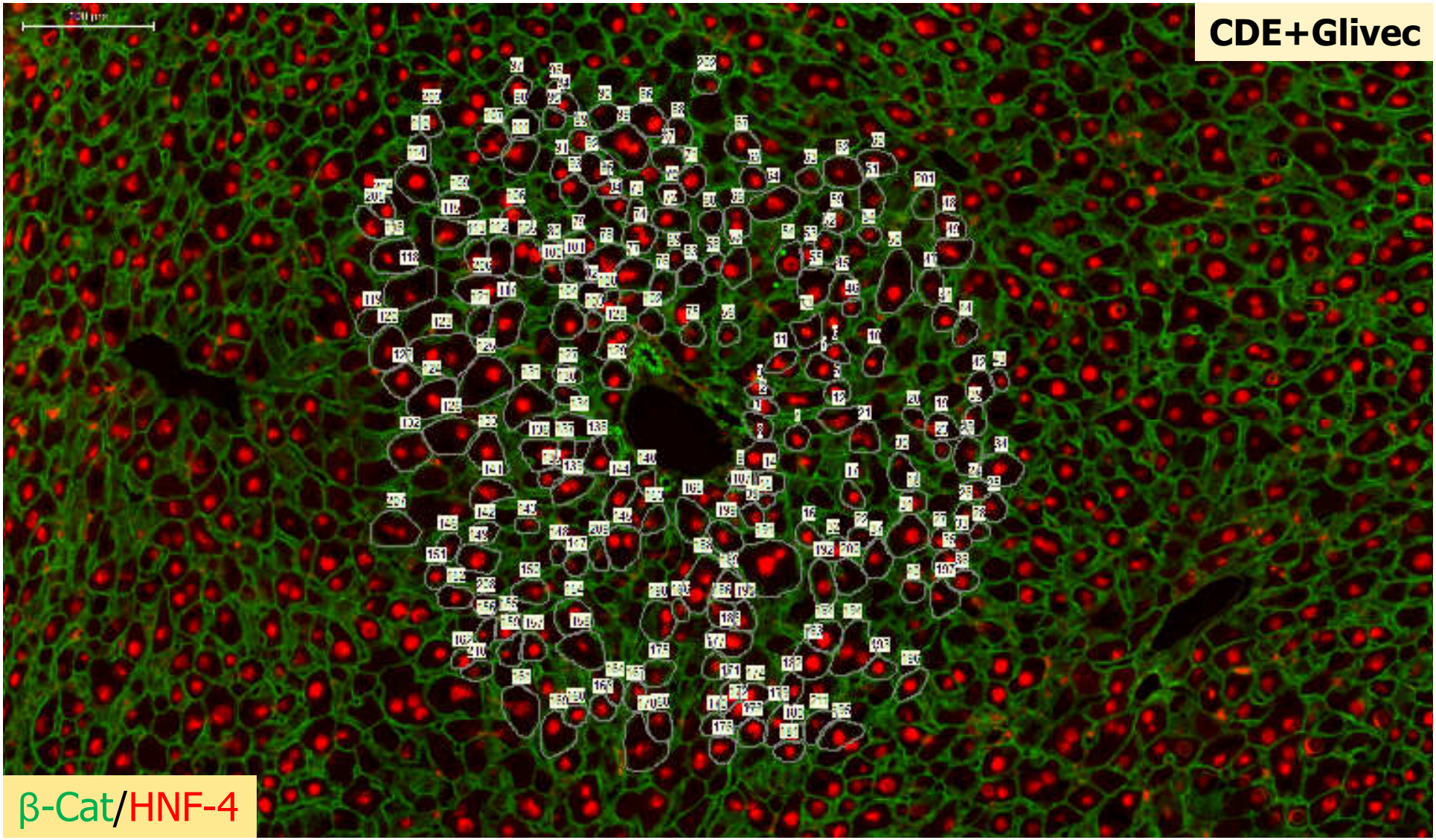
Experimental model

- CDE (cholin deficient ethionine supplemented diet is a well established model of ductular reaction
- HOW SIMULTANEOUS GLIVEC ADMINISTRATION INFLUENCES THE CDE INDUCED DUCTULAR REACTION?

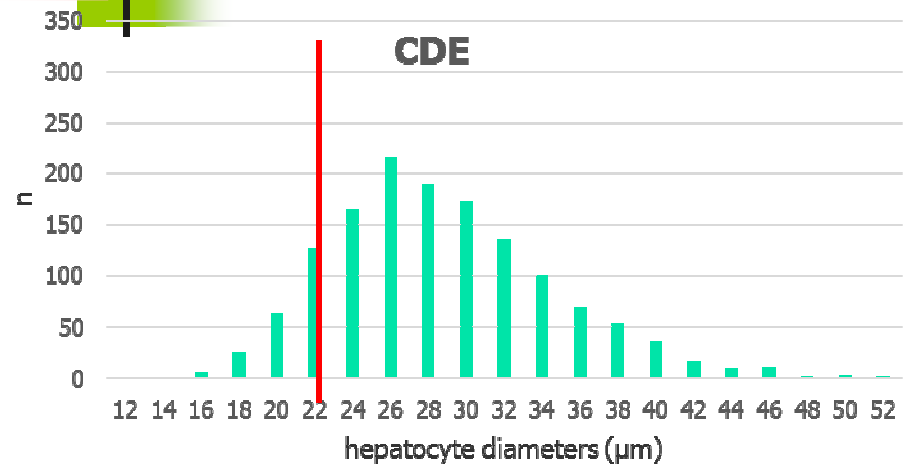

CDE
CDE+Glivec

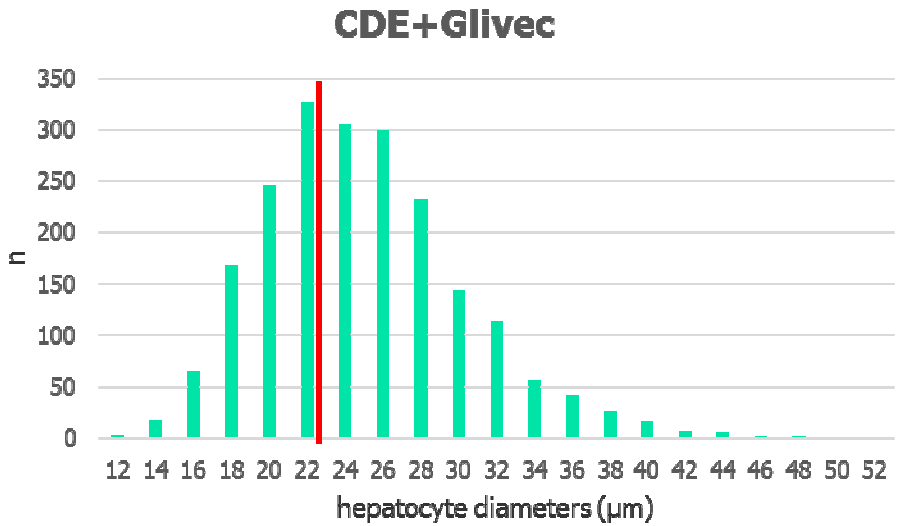


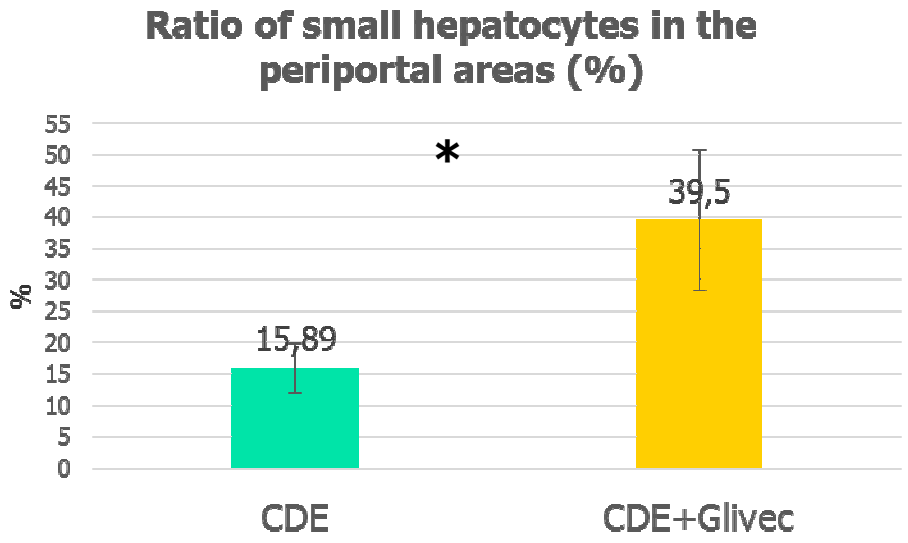
Quantitation of hepatocytic size



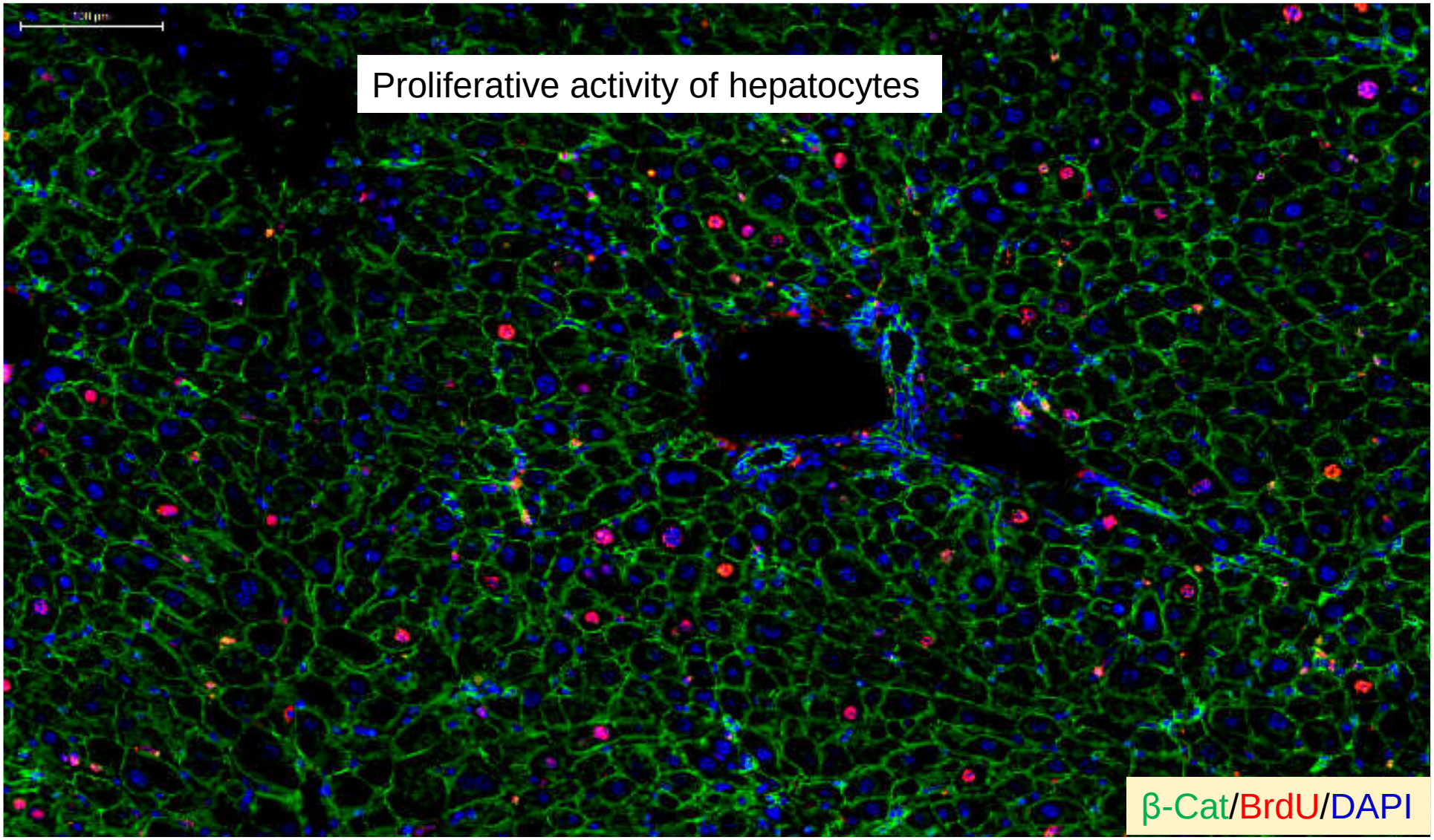
Distribution of hepatocytic size





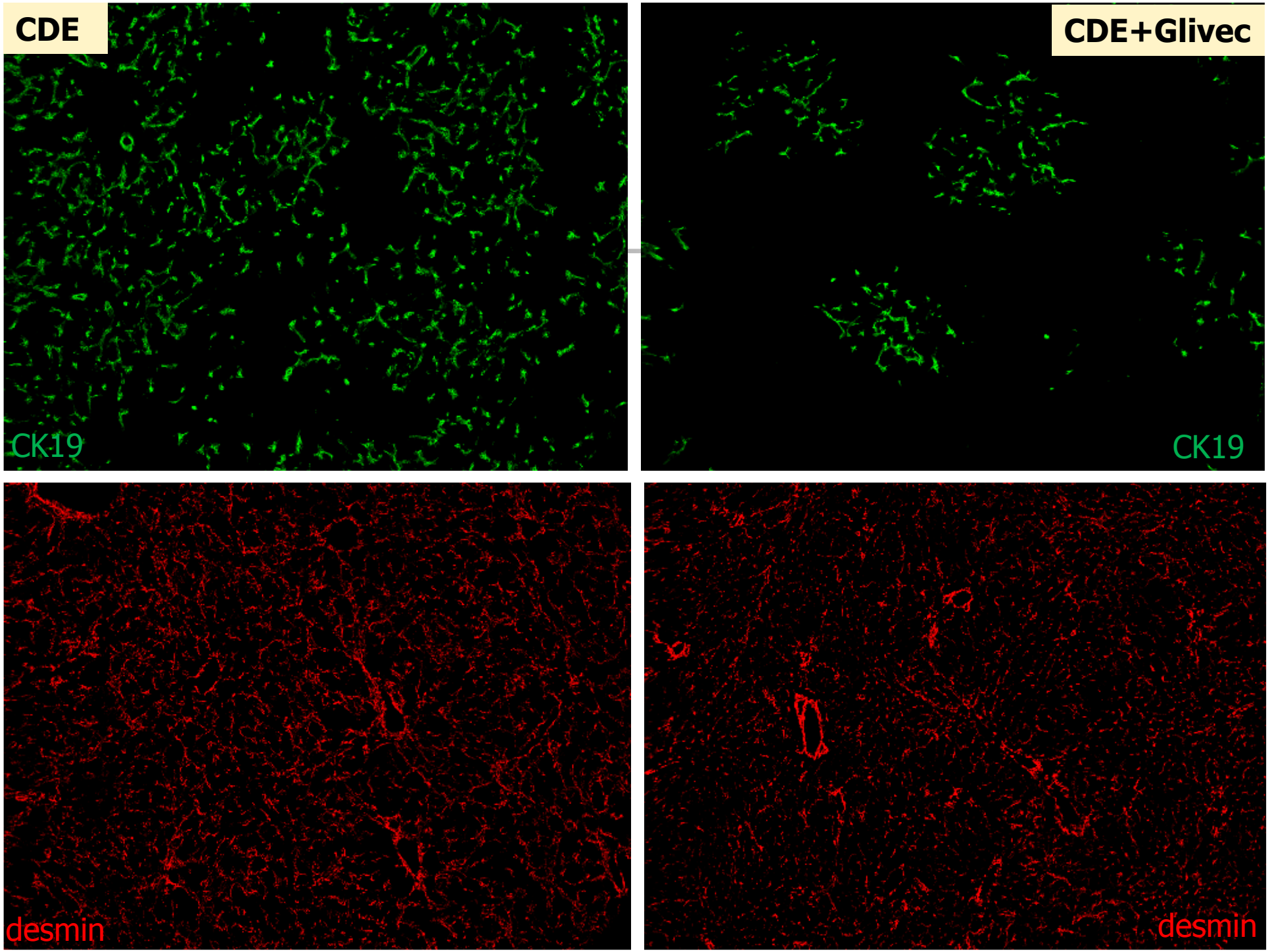


p=0,0286 (Mann-Whitney U test)

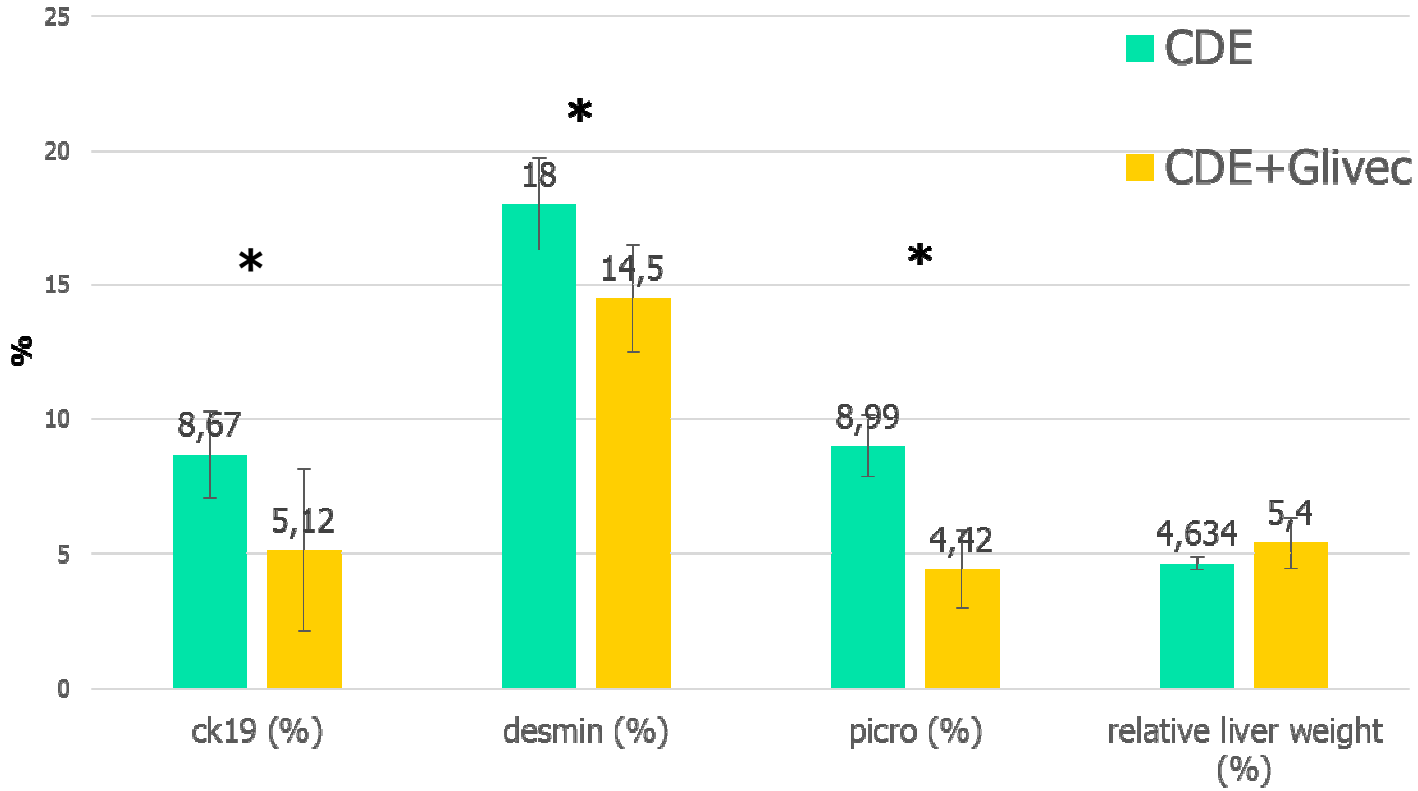


The ratio of BrdU positive large hepatocytes: 4,23±1,68%

The ratio of BrdU positive small hepatocytes: 11,15±1,13%


CDE
CDE+Glivec
CK19
CK19
desmin
desmin

Glivec reduces the extent of ductular reaction and fibrosis



p=0,0274 (Mann-Whitney U test)

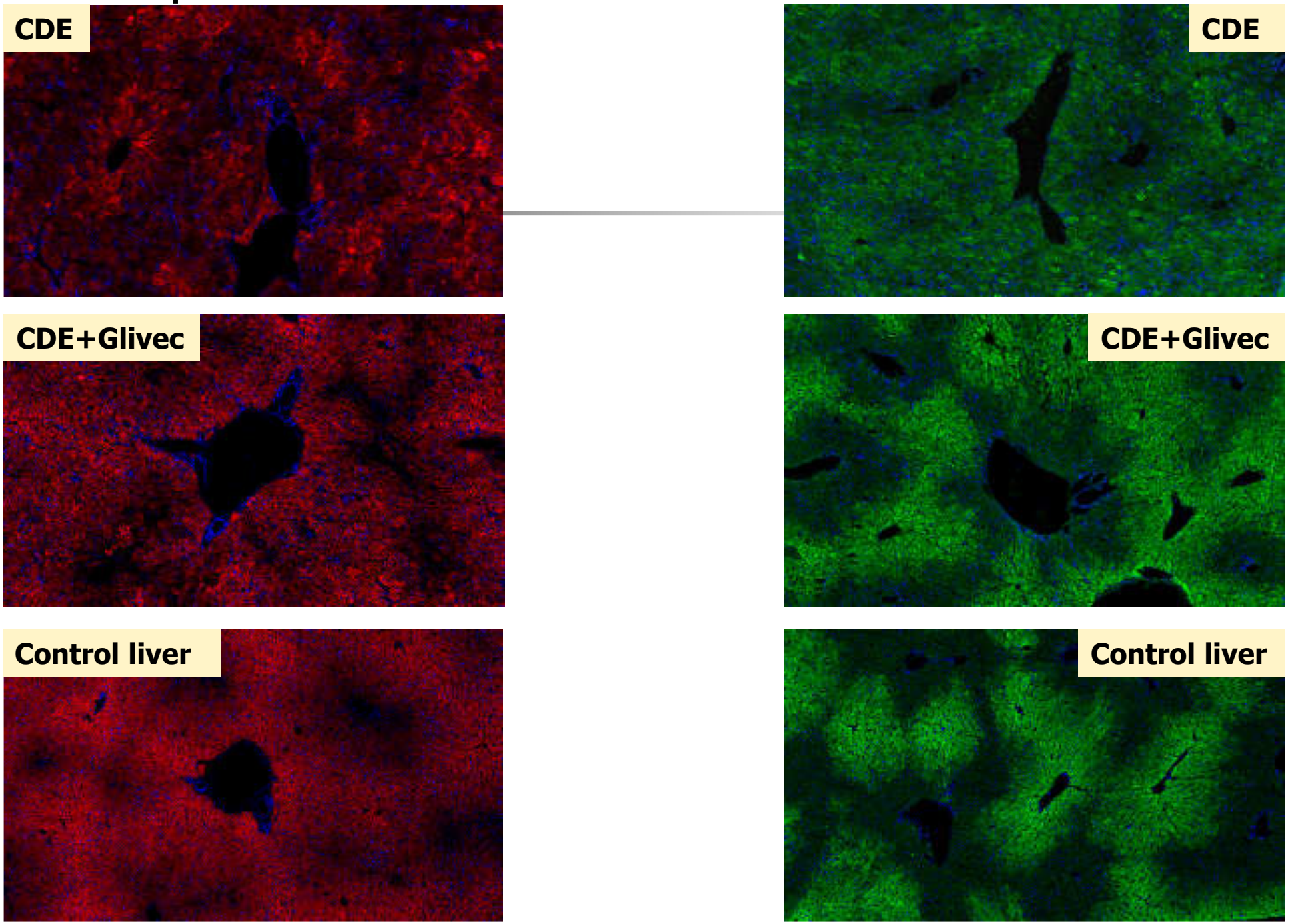
p=0,0017 (2-sided t-probe)

p=0,004 (Mann-Whitney U test)

p=0,0952 (2-sided t-probe)

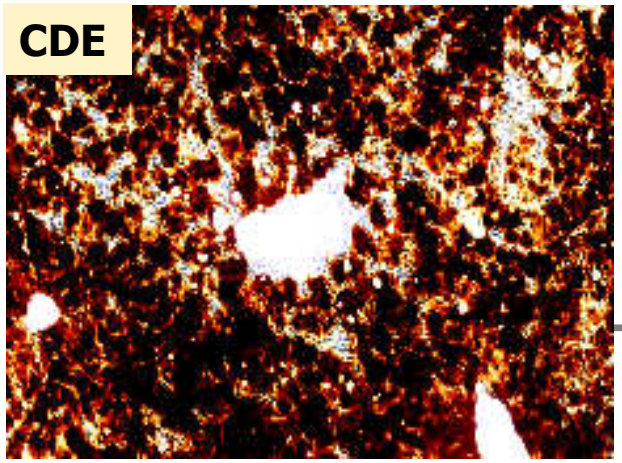
Streptavidin/DAPI

CYP IIE1/DAPI

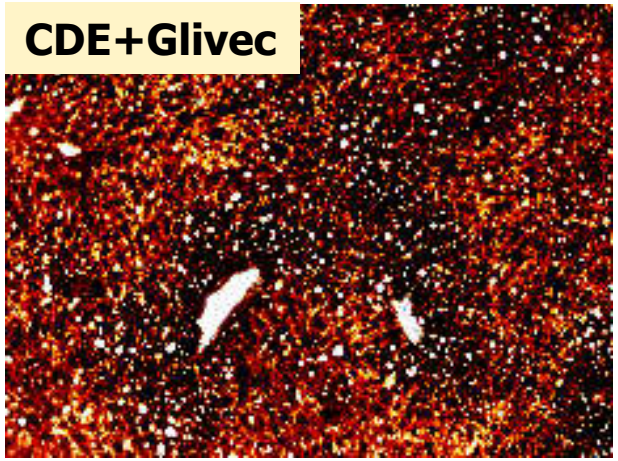


G6P

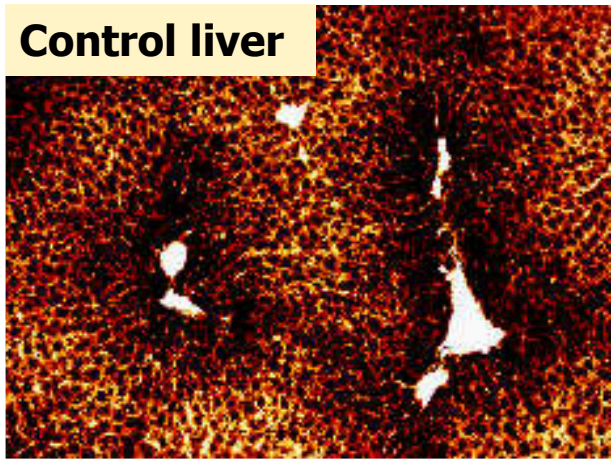
CDE



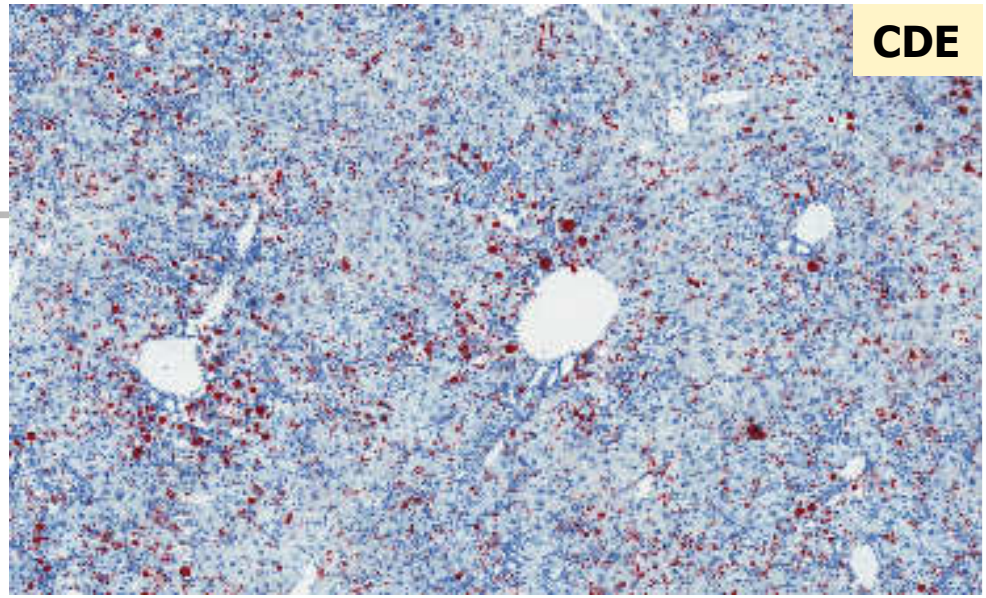
CDE+Glivec

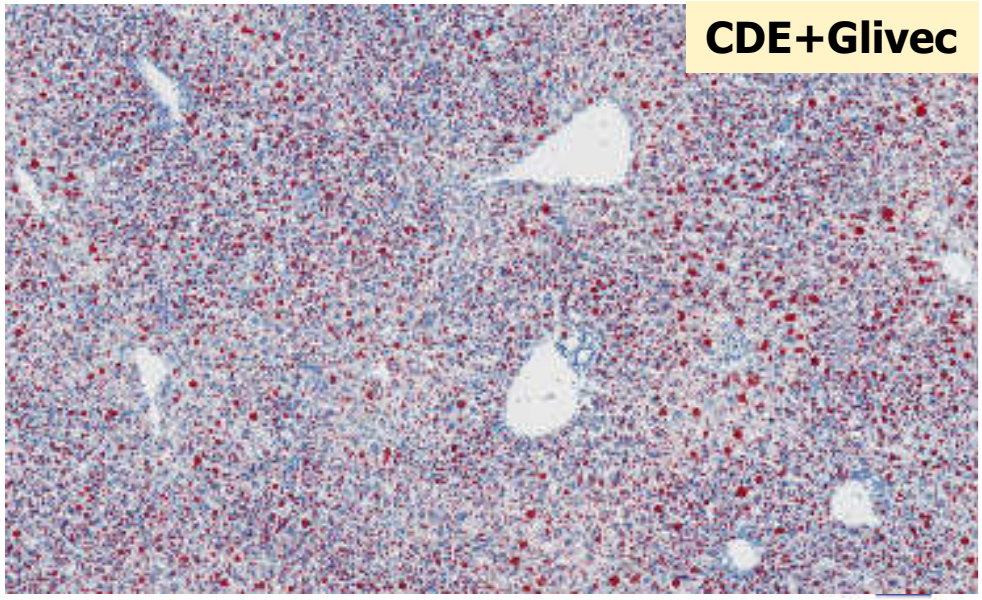


Control liver

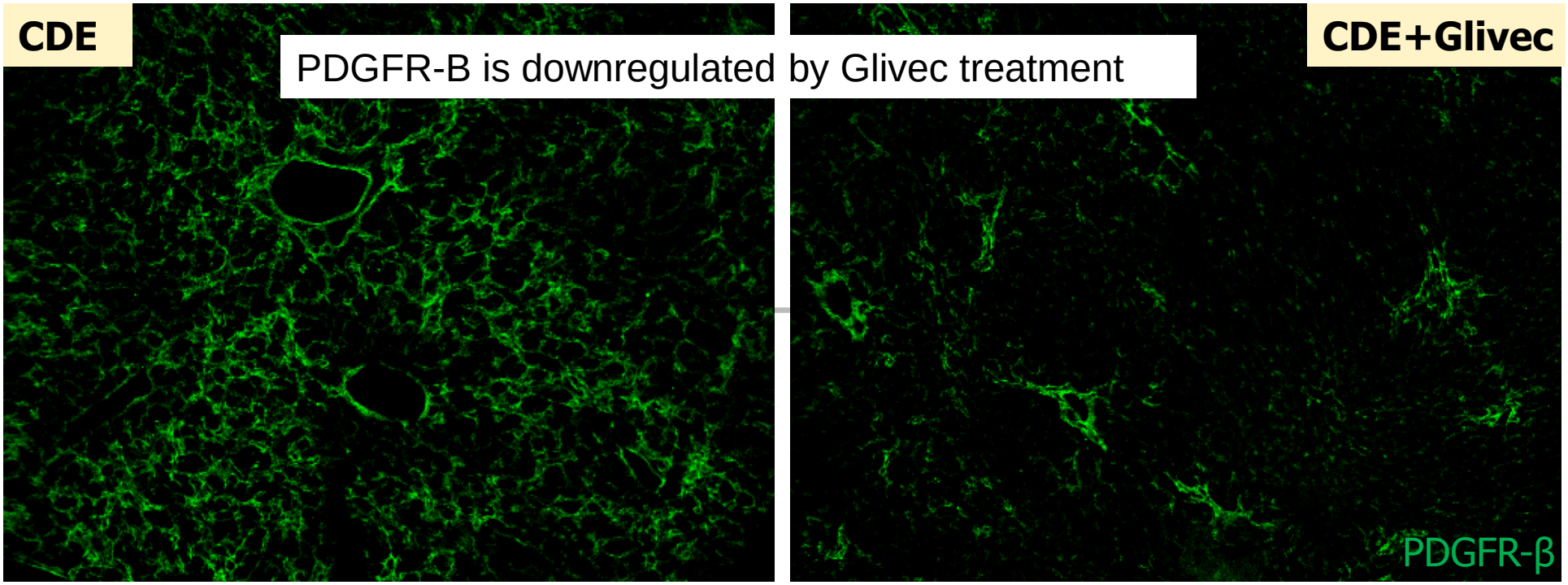


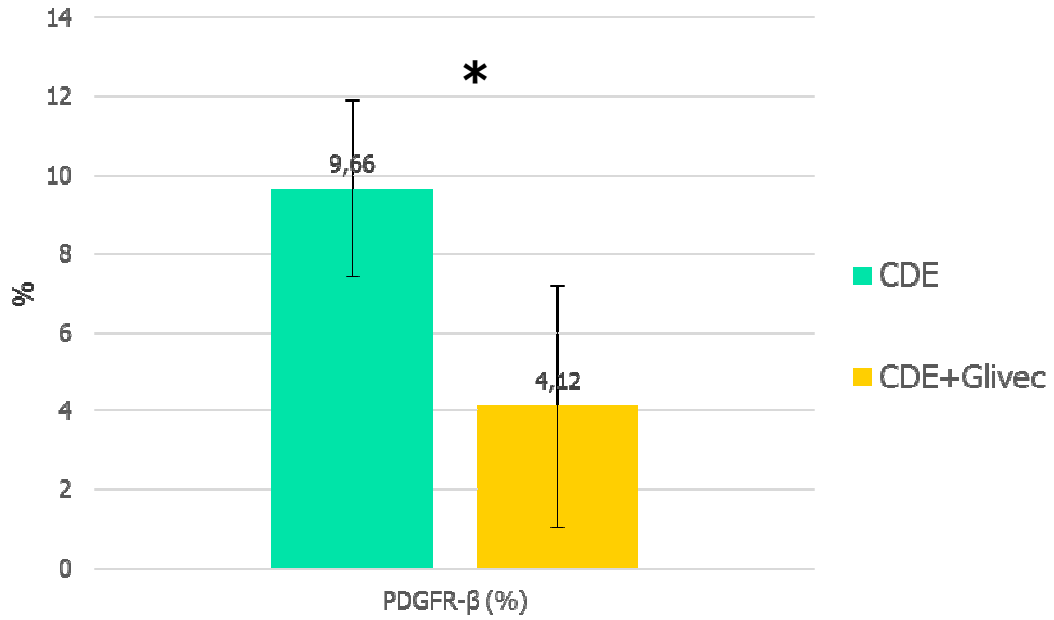
Oil Red O





PDGFR-B is downregulated by Glivec treatment





p=0,0019 (Mann-Whitney U test)

RESULTS

Glivec treatment in the CDE model:

Icreased the ratio of small hepatocytes,

Decreased the extent of ductular reaction,

Attenuated the fibrotic process,

Promoted the maintenance of metabolic zonation.

CONCLUSIONS

- Glivec promoted the progenitor cell driven regeneration of the liver
- It also attenuated the „side effects” of ductular reaction in the CDE experimental model.

Acknowledgement

Rókusz András

Dezső Kata

Paku Sándor

Sztodola András