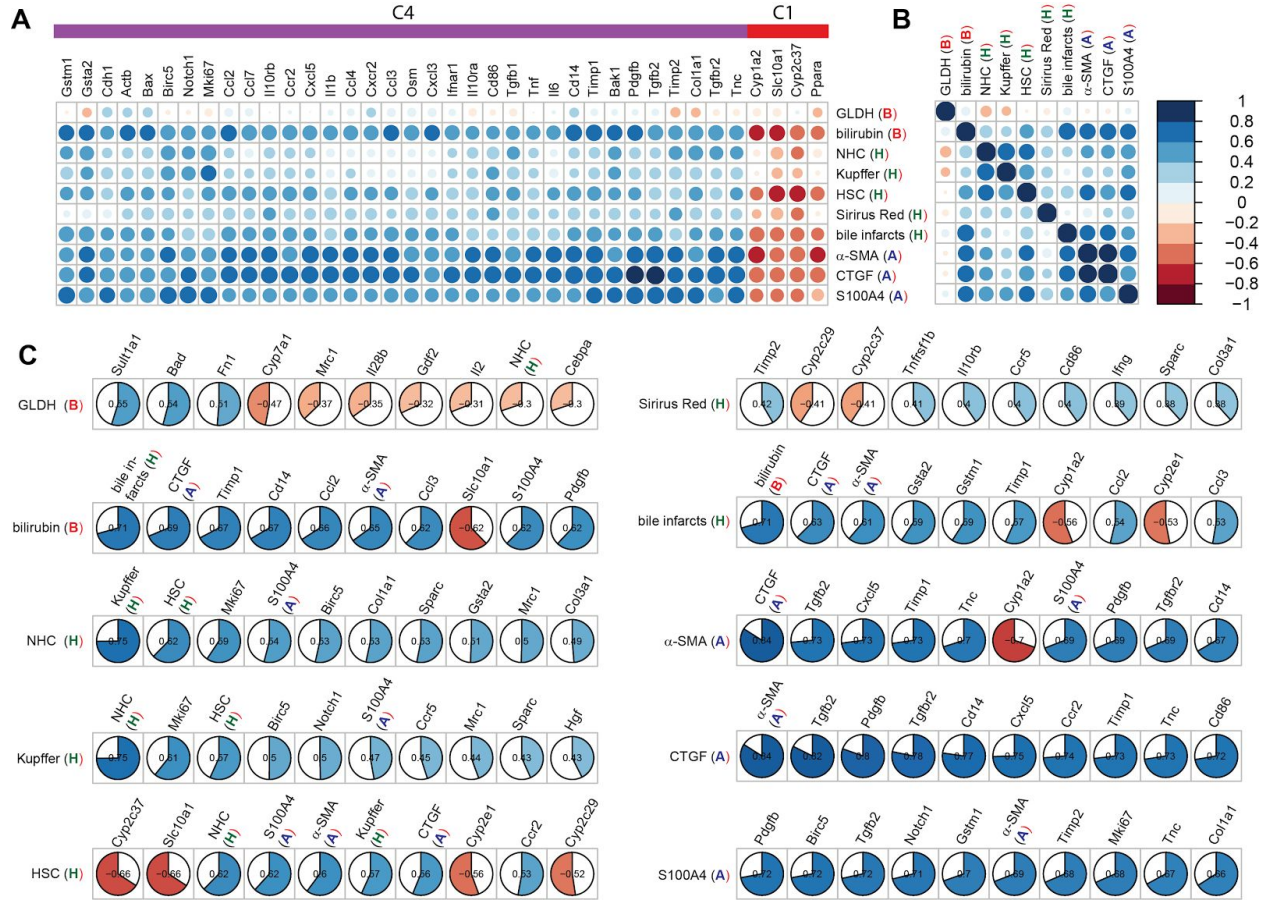


## ANOVA results

| Factor         | p-value               |     | p-value (Holm adjusted) |     |
|----------------|-----------------------|-----|-------------------------|-----|
| Cyp1a2         | 1.91342264023676E-016 | *** | 2.94667086596461E-014   | *** |
| bilirubin      | 3.27395955367953E-014 | *** | 5.00915811712969E-012   | *** |
| Il10rb         | 7.63982399859513E-014 | *** | 1.16125324778646E-011   | *** |
| Tgfb1          | 2.19724754091711E-013 | *** | 3.31784378678484E-011   | *** |
| Ccl2           | 2.32001535448977E-013 | *** | 3.48002303173466E-011   | *** |
| Cd86           | 4.43398094033834E-013 | *** | 6.60663160110413E-011   | *** |
| Ccr2           | 4.7207988695294E-013  | *** | 6.98678232690351E-011   | *** |
| Mrc1           | 4.76201704229549E-013 | *** | 7.00016505217438E-011   | *** |
| Tnfrsf1b       | 5.44303026552875E-013 | *** | 7.94682418767197E-011   | *** |
| Cxcl5          | 4.34564483500159E-012 | *** | 6.3011850107523E-010    | *** |
| CTGF           | 5.46635298072514E-012 | *** | 7.8715482922442E-010    | *** |
| Il10ra         | 1.15477077793218E-011 | *** | 1.65132221244301E-009   | *** |
| Gstm1          | 6.51380591994191E-011 | *** | 9.24960440631751E-009   | *** |
| Ccl7           | 2.43088335234461E-010 | *** | 3.4275455268059E-008    | *** |
| Ccr5           | 3.13926202190641E-010 | *** | 4.39496683066897E-008   | *** |
| Hgf            | 4.20334360409302E-010 | *** | 5.8426476096893E-008    | *** |
| Osmr           | 7.38949941761375E-010 | *** | 0.000000102             | *** |
| Ccl4           | 7.67090680670405E-010 | *** | 1.05091423251846E-007   | *** |
| Nr0b2          | 0.000000001           | *** | 1.30672786047445E-007   | *** |
| Tgfb2          | 1.27699003792023E-009 | *** | 1.72393655119231E-007   | *** |
| BrdU_HSC       | 1.56963992826678E-009 | *** | 2.10331750387749E-007   | *** |
| Ccl5           | 2.10407584924822E-009 | *** | 2.79842087950013E-007   | *** |
| Col1a1         | 3.35663234495581E-009 | *** | 4.43075469534167E-007   | *** |
| Ifnar1         | 5.93309462206502E-009 | *** | 7.77235395490518E-007   | *** |
| S100A4         | 7.12298809471991E-009 | *** | 0.000000926             | *** |
| Sparc          | 8.38363234548618E-009 | *** | 1.08148857256772E-006   | *** |
| Cyp2e1         | 1.18106363259919E-008 | *** | 1.51176144972696E-006   | *** |
| Cxcr2          | 1.39031297789528E-008 | *** | 1.76569748192701E-006   | *** |
| Ccr3           | 1.52418929058291E-008 | *** | 1.92047850613446E-006   | *** |
| Cd69           | 0.000000022           | *** | 2.75034504981931E-006   | *** |
| Cyp2c29        | 2.38412801732629E-008 | *** | 2.9563187414846E-006    | *** |
| Gsta2          | 3.18037362655874E-008 | *** | 3.91185956066725E-006   | *** |
| Tnf            | 0.000000036           | *** | 0.000004395             | *** |
| Gdf2           | 4.95804294192854E-008 | *** | 5.99923195973354E-006   | *** |
| Il1b           | 6.12872857427699E-008 | *** | 7.35447428913239E-006   | *** |
| Ifng           | 6.36729003696979E-008 | *** | 0.000007576             | *** |
| Osm            | 6.36637501453233E-008 | *** | 0.000007576             | *** |
| Ccl3           | 7.3549197590383E-008  | *** | 8.60525611807481E-006   | *** |
| Il13           | 8.08157001605371E-008 | *** | 9.37462121862231E-006   | *** |
| Cxcr1          | 9.41283110829526E-008 | *** | 1.08247557745396E-005   | *** |
| Cyp2c37        | 9.65026773866885E-008 | *** | 1.10013052220825E-005   | *** |
| Cd14           | 1.0281684108002E-007  | *** | 1.16183030420422E-005   | *** |
| Col3a1         | 1.8165609631441E-007  | *** | 2.03454827872139E-005   | *** |
| Tnfrsf1a       | 3.02825864088077E-007 | *** | 3.36136709137765E-005   | *** |
| Il2            | 4.43711365153111E-007 | *** | 4.88082501668422E-005   | *** |
| Ifnb1          | 4.50419343820152E-007 | *** | 4.90957084763966E-005   | *** |
| Egf            | 4.55680005521404E-007 | *** | 4.92134405963116E-005   | *** |
| Il4            | 4.60199593762361E-007 | *** | 4.92413565325726E-005   | *** |
| Il28b          | 4.64575161516398E-007 | *** | 0.000049245             | *** |
| Il10           | 4.6663710756229E-007  | *** | 0.000049245             | *** |
| Slc10a1        | 5.10222512673073E-007 | *** | 5.30631413179996E-005   | *** |
| Timp2          | 6.11614358775742E-007 | *** | 6.29962789539014E-005   | *** |
| Cxcl3          | 0.0000000675          | *** | 6.88516389428801E-005   | *** |
| Ccl8           | 1.23279663549998E-006 | *** | 0.0001245125            | *** |
| Ctgf           | 1.33622451654719E-006 | *** | 0.0001336225            | *** |
| Gstp1          | 1.40917342020316E-006 | *** | 0.0001395082            | *** |
| Ppara          | 1.68310618760453E-006 | *** | 0.0001649444            | *** |
| Ifnar2         | 1.89821207406025E-006 | *** | 0.0001841266            | *** |
| Il6            | 2.35209617540156E-006 | *** | 0.0002258012            | *** |
| Il17a          | 2.58037790633237E-006 | *** | 0.0002451359            | *** |
| Bad            | 4.12522559223528E-006 | *** | 0.0003877712            | *** |
| Timp1          | 4.67845283519821E-006 | *** | 0.0004350961            | *** |
| Cdh1           | 0.00000492            | *** | 0.0004526391            | *** |
| Cebpa          | 5.47343865919207E-006 | *** | 0.0004980829            | *** |
| alpha.SMA      | 0.000005638           | *** | 0.0005074204            | *** |
| BrdU_NHC       | 0.000006005           | *** | 0.0005344464            | *** |
| Cdh2           | 6.17914742457919E-006 | *** | 0.000543765             | *** |
| BrdU_SiriusRed | 8.81983941044958E-006 | *** | 0.000767326             | *** |
| Pdgfb          | 9.03245409952277E-006 | *** | 0.0007767911            | *** |
| Il6st          | 1.03707632879727E-005 | *** | 0.0008815149            | *** |
| Fn1            | 1.45776163221202E-005 | *** | 0.0012245198            | **  |
| Mki67          | 1.77462324214441E-005 | *** | 0.0014729373            | **  |
| Ifna1          | 1.80502947443697E-005 | *** | 0.0014801242            | **  |
| Egfr           | 1.98831180442088E-005 | *** | 0.0016105326            | **  |
| BrdU_Kupffer   | 2.47061167978283E-005 | *** | 0.0019764893            | **  |

|              |                       |     |              |    |
|--------------|-----------------------|-----|--------------|----|
| Tnc          | 2.61121496644436E-005 | *** | 0.0020628598 | ** |
| Ugt1a1       | 3.57068529161741E-005 | *** | 0.0027851345 | ** |
| Sult1a1      | 3.92227409891161E-005 | *** | 0.0030201511 | ** |
| GLDH         | 5.71185646136636E-005 | *** | 0.0043410109 | ** |
| Notch1       | 0.000060164           | *** | 0.0045123018 | ** |
| Met          | 6.80346774563997E-005 | *** | 0.0050345661 | ** |
| Cyp7a1       | 0.00013651            | *** | 0.0099652314 | ** |
| Cyp24a1      | 0.0001391831          | *** | 0.0100211829 | *  |
| Tgfb2        | 0.0001542364          | *** | 0.010950784  | *  |
| Birc5        | 0.0002454637          | *** | 0.0171824558 | *  |
| Actb.y       | 0.000280664           | *** | 0.019365815  | *  |
| Bak1         | 0.0004077548          | *** | 0.0277273274 | *  |
| Bax          | 0.0004371327          | *** | 0.0292878876 | *  |
| Rarres1      | 0.0005491381          | *** | 0.0362431116 | *  |
| bileInfarcts | 0.0005904178          | *** | 0.0383771539 | *  |
| Cyp3a11      | 0.0008410363          | *** | 0.0538263241 | 0  |
| Sult1b1      | 0.0009257764          | *** | 0.058323915  | 0  |
| Cyp4a10      | 0.0011244464          | **  | 0.069038815  | 0  |
| Pparg        | 0.0011135293          | **  | 0.069038815  | 0  |
| Hk2          | 0.0012711725          | **  | 0.0762703529 | 0  |
| ALT          | 0.0015159716          | **  | 0.0894423215 | 0  |
| Smad6        | 0.0016656545          | **  | 0.0966079586 | 0  |

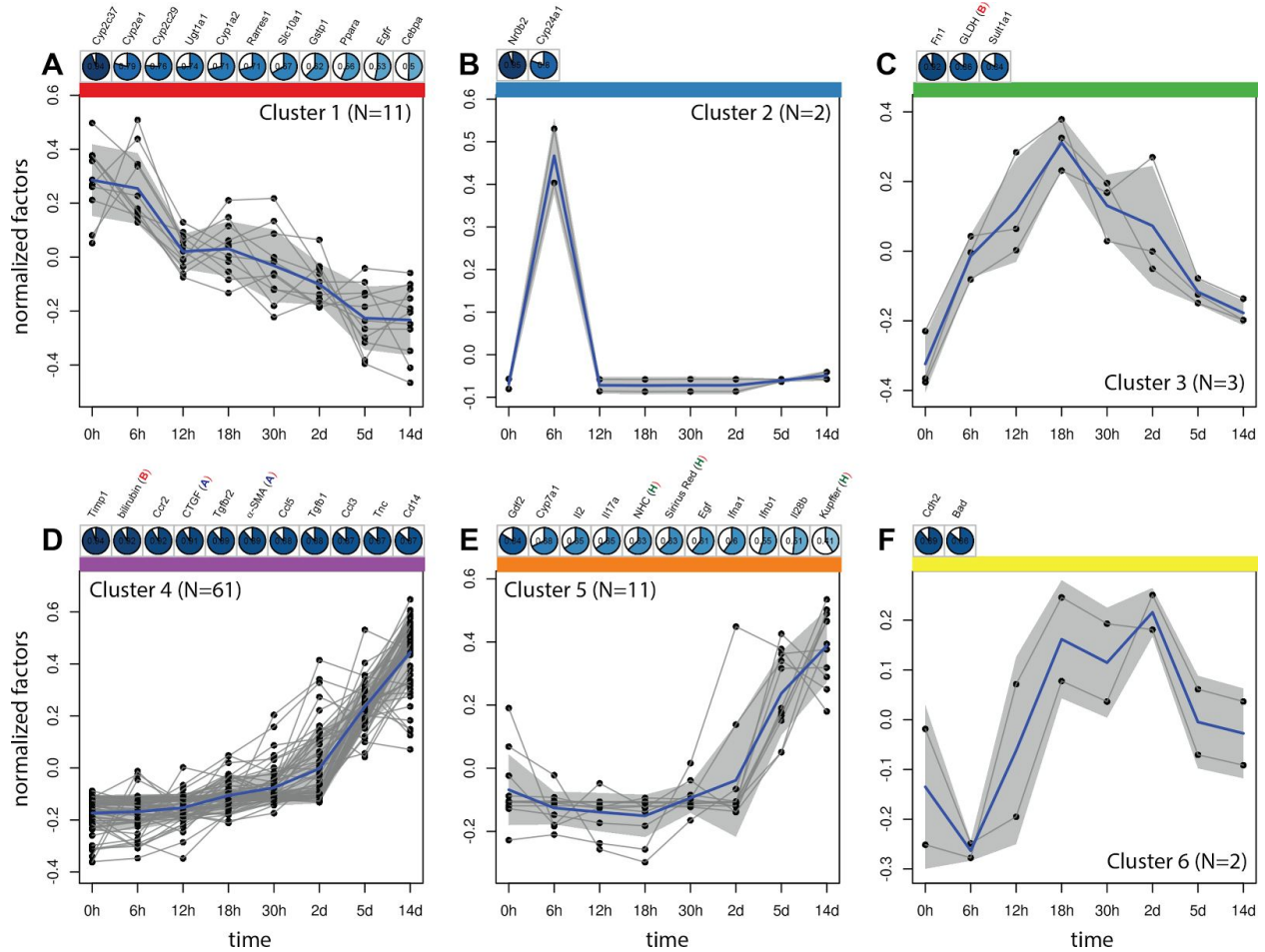




**Figure 8: Correlations of histological, biochemical and antibody factors.** **A** Correlation between histological, biochemical and antibody factors and gene expression data. YS3 correlation was calculated between histopathological factors (rows) and the subset of ANOVA filtered factors (data corresponds to a subset of Figure 7). Only columns with at least one YS3 correlation of  $\text{abs(YS3)} \geq 0.6$  are shown. Positive correlation in blue, negative correlation in red analog to Figure 7, with the area of circles corresponding to the correlation coefficients. Numerical values are provided in Supporting Information S2. **B** Highest absolute correlations between the individual histological, biochemical and antibody factors and the gene expression data. Data sorted from left to right by  $\text{abs(YS3)}$ . Color and size of the filled pie correspond to the respective correlation.

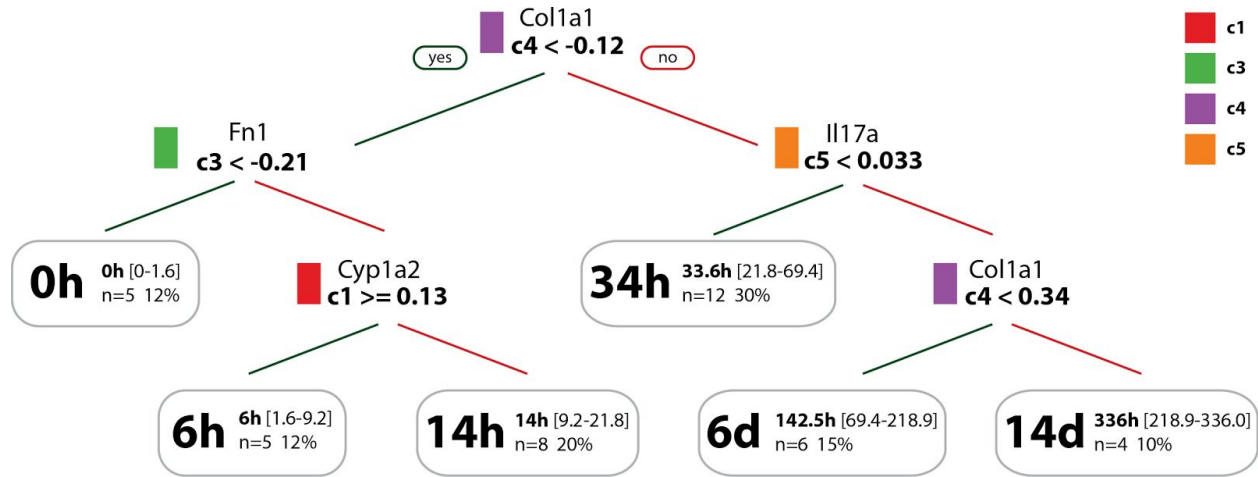
TODO: Left align the names: GLDH, ...



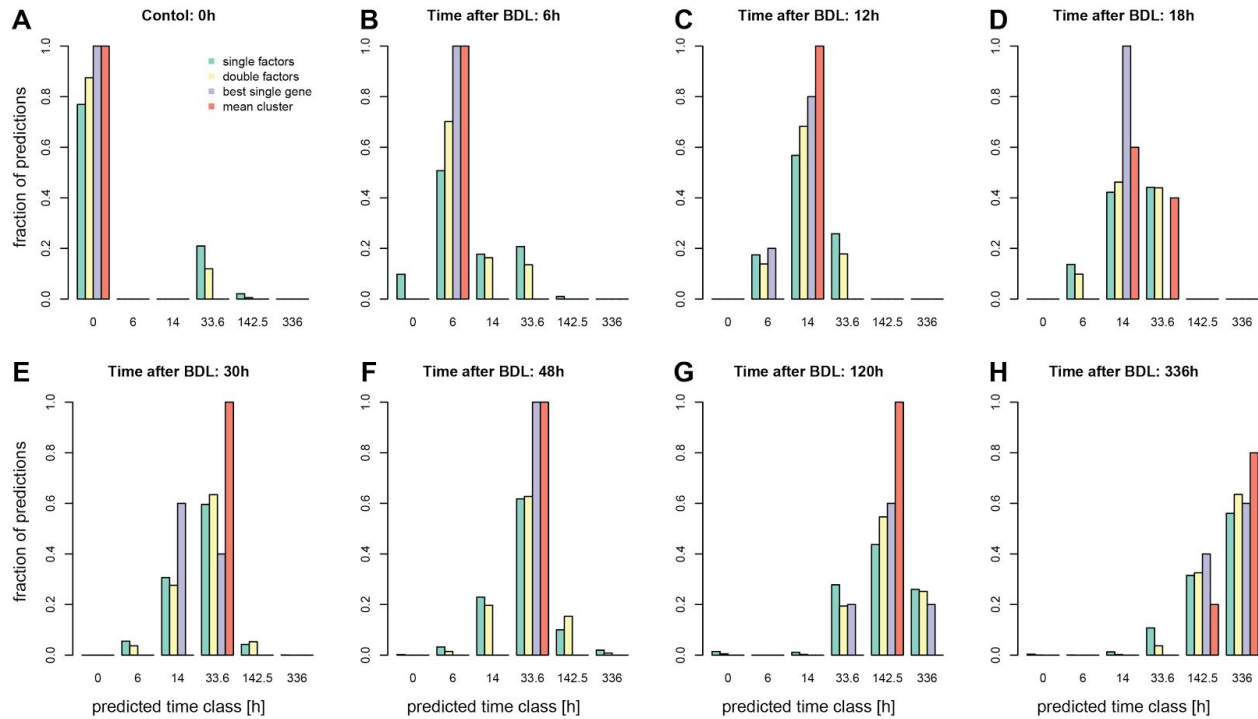


**Figure 9: Main time course clusters in BDL.** The 6 top time course clusters based on YS3 correlation with hierarchical clustering based on complete linkage. Cluster colors analog to Figure 7. The mean cluster time course (averaged over all factors and repeats) is depicted in blue with grey area corresponding to SD for the cluster members at the respective time points. Cluster members are enumerated for all classes with exception for the largest cluster, cluster 4 with N=61 members (Gstm1, Gsta2, Ccl2, Cd86, Met, Tnfrsf1a, Il1b, Cxcl5, Cxcr1, Ifnar1, Osmr, Tgfb1, Ifng, Ccl4, Ccl5, Ccr3, Il13, Tnfrsf1b, Ccl7, Osm, Cd69, Il10rb, Cd14, Cxcr2, Tnf, Il10ra, Il10, Ccr2, Hgf, Ifnar2, Mrc1, Ccr5, Ccl3, Il6, Actb.y, Il4, Ccl8, Cxcl3, Il6st, Birc5, Sparc, Col1a1, Tgfb2, Timp1, Pdgb, Cdh1, Timp2, Bak1, Ctgf, Notch1, Tnc, Bax, Mki67, Tgfb2, Col3a1, bilirubin (B), HSC (H), bile infarcts (H),  $\alpha$ -SMA (A), CTGF (A), S100A4 (A))

TODO: use vector graphics for the clusters



**Figure 11: Decision trees based on clusters.** Regression tree for the prediction of time phases after BDL based on the correlation time course clusters. The decision tree for the mean clusters and the best tree based on gene probes from the individual clusters are depicted. The regression tree results in 6 time classes 0h, 6h, 14h, 24h, 6d, 14d. For every time class the respective information about mean time of the class, range and number and percentage of samples falling into the class are listed. The best tree allowing also histological, biochemical and antibody factors is highly similar, only replacing Col1a1 with S100A4 for cluster c4.

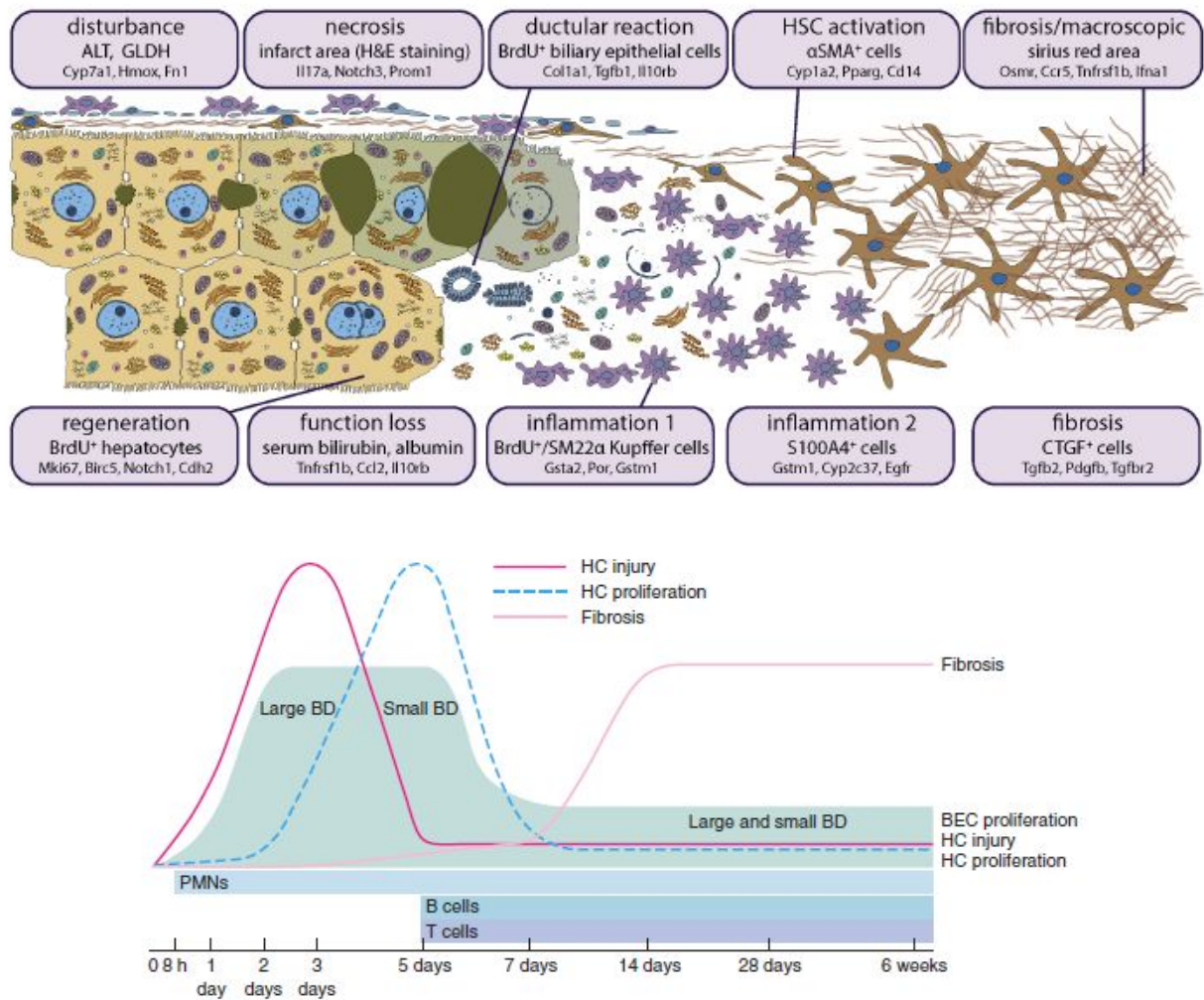


**Figure 12 Predictive performance of decision tree.** The predictive performance of the regression tree was evaluated using mean cluster data, all single factors from the individual clusters and a random sample of 2 factors from each cluster. In addition the results for the best single factor tree (depicted in Figure 10) are shown.

TODO: better colors, i.e gray for the mean single and double predictions

TODO: add boxplots/STD for the single & double predictions

TODO: bigger labels



**Fig. 9** Overview of dynamic changes following bile duct ligation in mice. BD, bile duct; BEC, biliary epithelial cell; HC, hepatocyte; PMN, polymorphonuclear leucocyte

{Georgiev2008}

**Figure 12: Outline of the disease process.** Each box is dedicated to a specific disease aspect (first line) which is represented by a commonly known marker (second line) or several markers. Below (in small font) the genes are shown whose expression is correlated to the factor above.

TODO: Update the factors in the groups based on clustering results and correlation (not necessarily the same results for all)