1 Supplementary Material and Methods

1.1 Gene expression datasets

A library of 109 genomewide mRNA expression patterns was compiled from four different studies (Figure 1a): 70 samples from a time series of expression data from liver samples of B6C3F1 vehicle- (i.e. control) or PB-treated mice at +1, +3, +7, +14, +28, +57 and +91 days of dosing (5 replicates) [1]; 8 mRNA expression patterns in livers of wild-type and hepatocyte-specific β-catenin knockout C3H/N [2] animals; 13 mRNA expression patterns in livers of wild-type and CAR knock-out C3H/N animals DEN-initiated at 5 weeks of age prior to 23 weeks of PB -or vehicle-treatment [3]. Datasets on global mRNA expression patterns (18 samples) from liver tumors and corresponding surrounding normal tissue of C3H/N animals DEN-initiated at 4 weeks of age prior to 35 weeks of PB- or vehicle-treatment were available to us from IMI-MARCAR partners (Unterberger et al, (2013), manuscript submitted). Screening the tumors for mutations in Ha-ras, B-raf and Ctnnb1 (i.e. the β-catenin coding gene) confirmed that promoted tumors (from animals exposed to PB) were mutated in Ctnnb1 while non-promoted tumors were mutated in Ha-ras (data not shown, Unterberger et al, 2013). In all four studies gene expression was profiled using Affymetrix GeneChip MOE-4302 (Affymetrix, Santa Clara, CA) containing approximately 43,000 probe sets.

1.2 Affymetrix GeneChip processing

The analysis of the micro-array data was done with the R statistical package version 2.13 (2005) and Bioconductor libraries version 1.4.7 [4]. The four original data-sets containing Affymetrix CEL files were normalized independently using the Robust Multichip Average (RMA) implementation of the algorithm available in R/Bioconductor [4], producing four expression matrices, and the quality of the experiments was assessed using diverse statistics implemented in the package arrayQualityMetrics for R/Bioconductor [5].
2 Supplementary Results

2.1 Regulators associated with termination of developmental liver growth ($\vec{v}_1$)

To determine motifs underlying the four characteristic modes identified in this study, we selected motifs which contributed and correlated the most with each of the four singular vectors (Figure 3c,d,e,f). In this way we obtained, for each of the 4 singular vectors, two clusters of motifs with similar activity profiles, i.e. one correlating negatively with the singular vector, and one correlating positively (Figures 3d,f). We further refined the selection of the motifs associated with first singular vector as follows: 1) removing motifs for which the overall significance was lower than $z < 1.5$ and 2) removing motifs whose cognate TFs were not expressed in the liver (log-expression less than 6.0) $\log_{2} z \leq 6.0$. This lead to the identification of 6 motifs motifs (Supplementary Table S1).

As originally observed in [1], completion of the post-natal liver development process occurs during the early PB-treatment time course, consisting in both hepatocyte proliferation at early stage, and progressive induction of liver-specific genes [6, 7]. We here identify key regulators of these two processes: 1. we show that post-natal liver growth (that decreases over time) is regulated by known regulators of cell proliferation such as the E2F family of TFs [8, 9, 10], SRF [11] and Myc [12, 13]; predicted target genes of these motifs have functions related to cell cycle and DNA replication (Supplementary Figure S6b), confirming the role of these regulators in cell proliferation. 2. We show that post-natal liver differentiation (which increases over time) is partly regulated by AHR, a known regulator of drug-metabolizing genes and transporters [14, 15, 16, 17] that has been shown to play key role in liver development [18]. Thus, the main biological process associated positively with the first singular vector is cellular proliferation associated with post-natal liver growth for the first two weeks of the time course. Conversely, the targets of the motifs that are negatively associated with the first singular vector, i.e. corresponding to genes that increase their expression after the first two weeks, are enriched for functions associated with hepatocyte terminal differentiation, such as ‘liver development’, ‘drug metabolism’ and ‘transcriptional regulation’.

2.2 Singular value decomposition analysis of the activity matrix of the CAR KO data-set

In order to identify and quantify the sources of motif activity changes in the CAR KO data-set, we performed Singular Value Decomposition (SVD) of the activities of the 189 motifs across the four conditions (PB- and vehicle treated livers from wild-type and CAR KO mice). Over 50% of the variance in the activity matrix was explained by the first two components of the SVD as evidenced by the spectrum of singular values (Figure S6a).

In order to facilitate the biological interpretation of the singular vectors, we plotted the averaged activities of the right singular vectors $\vec{v}_k$ over each of the four sample groups and further identified regulatory motifs whose activity profiles correlate most strongly (either positively or negatively) with the activity profile of the singular vector. Visualization of the averaged activity of the first two singular vectors $\vec{v}_1$ and $\vec{v}_2$ in each of the four sample groups is shown in Figure S6b and scatter plots of the correlations $\rho_i$ and projections $p_i$ of all motifs $i$ with the first and second right singular vectors are shown in Figure S6c.

The first right singular vector accounts for 33% of the variance and is characterized by a positive activity upon PB treatment in wild-type animals only. Given the absence of positive activity in CAR KO treated animals, we propose that this component represents the liver response to PB that is CAR-dependent. Moreover motifs which contribute and correlate most strongly with the first singular vector (TBP, NFE2, REST, GLI1,2,3, FOSL2, ELK1,2, and ZNF143) are all down-stream of CAR signaling under PB treatment (Table S2) except CTCF, RXRG-dimer and STAT5(A,B), further supporting the association of this component with the CAR-dependent liver response to PB treatment.

The second right singular vector accounts for 18% of the variance and is characterized by 1) a lower activity in wild-type liver samples compared to CAR KO samples, and 2) by an activity further lowered upon PB treatment in both wild-type and CAR KO samples (Figure S6b). We propose that this component represents the basal liver activity down-stream of CAR that is further exacerbated upon PB treatment. However the motifs that contribute and correlate most strongly with the second singular vector do not coincide with any of the 5 motifs identified by differential motif activity analysis as down-stream of CAR signaling under physiological condition (Table S2). Furthermore the average activities have large associated error-bars for each sample group, indicating that the interpretation of this component must be considered with caution.

In conclusion, the SVD-based analysis of the activity matrix of the CAR KO data-set indicates that the major
source of motif activity changes in these liver samples is the CAR-dependent liver response to PB treatment. This result is in line with the analysis based on differential motif activity. Importantly, prior biological knowledge indicates that at least two biological processes are occurring in this system, i.e. the CAR KO effect and the xenobiotic response to PB treatment. Differential motif activity previously showed only a very minor CAR KO effect (only 5 motifs identified as down-stream of CAR signaling under physiological condition, see Table S2) that may explain the absence of strong association of any component with this biological process.

2.3 Singular value decomposition analysis of the activity matrix of the tumor study data-set

In order to identify and quantify the sources of motif activity changes in the tumor data-set, we performed Singular Value Decomposition (SVD) of the activities of the 189 motifs across the four conditions (PB- and vehicle treated normal and tumorigenic liver samples). Over 57% of the variance in the activity matrix was explained by the first two components of the SVD that are the two significant components of the matrix, as evidenced by the spectrum of singular values (Figure S7a).

In order to facilitate the biological interpretation of the singular vectors, we plotted the averaged activities of the right singular vectors \(v_{ks}\) over each of the four sample groups and further identified regulatory motifs whose activity profiles correlate most strongly (either positively or negatively) with the activity profile of the singular vector. Visualization of the averaged activity of the first two singular vectors \(\vec{v}_1\) and \(\vec{v}_2\) in each of the four sample groups is shown in Figure S7b and scatter plots of the correlations \(\rho_i\) and projections \(p_i\) of all motifs \(i\) with the first and second right singular vectors are shown in Figure S7c.

The first right singular vector accounts for 32% of the variance (Figure S7a) and is characterized by 1) a higher activity in PB-treated samples relative to non-treated samples, 2) an increased positive activity in promoted tumor samples relative to all other sample groups (normal treated and non-treated samples, and non-treated tumor samples) and 3) a slight decreased activity in non-promoted tumor samples relative to surrounding normal tissue (Figure S7b). Moreover several motifs which contribute and correlate most strongly with the first singular vector (NFE2, E2F1-5, PBX1, and ESR1) as depicted in Figure S7c, have been identified as specific regulators of promoted tumors by differential motif activity analysis (see Table S4). These results indicate that motifs associated with this component are generally associated with a response to PB treatment which is further 1) exacerbated in promoted tumor samples and 2) inhibited in non-treated tumor samples, suggesting that the first component captures motifs associated with biological pathways underlying promoted tumors that are already up-regulated upon PB treatment and down-regulated in non-promoted tumors.

The second right singular vector accounts for 25% of the variance (Figure S7a) and is characterized by an overall decreased activity in tumor samples relative to normal samples, irrespective of the PB treatment (Figure S7b); this suggests that the second component captures motifs associated with biological pathways underlying tumorigenesis. It is however noteworthy that none of the motifs which contribute and correlate most strongly with the second singular vector (Figure S7c) were identified as regulators of tumorigenesis by differential motif activity analysis (Table S3). One explanation for this could be a strong variability in activity profiles leading to low Z-value of differential activity.

In conclusion the SVD-based analysis of the activity matrix allows for the identification of 1) regulators of promoted tumors (first component) which are consistent with those identified by differential motif activity analysis, and 2) regulators of liver tumorigenesis, which were not identified by differential motif activity analysis, potentially due to high noise to signal ratio.
Figure S1: Selection of representative biological terms and processes associated with the predicted target genes of motifs which activities were significantly (a) higher or (b) lower in promoted tumors relative to surrounding treated normal tissue, and in non-promoted tumors relative to surrounding non-treated normal tissue (Supplementary Table S3). Bars are colored according to motif to which the target genes are associated with. Bar height indicates significance of functional enrichment as it represents the $-\log_{10}(P\text{-Value})$ of functional enrichment in the given biological term or process as obtained from the DAVID Bioinformatic Resource (Database for Annotation, Visualization and Integrated Discovery) [19, 20] version 6.7, sponsored by the National Institute of Allergy and Infectious Disease (NIAID), NIH.
Figure S2: Selection of representative biological terms and processes associated with the predicted target genes of motifs which activity was significantly (a) lower or (b) higher in promoted tumors relative to surrounding treated normal tissue, but that did not change in non-promoted tumors relative to surrounding non-treated normal tissue (Supplementary Table S4). Bars are colored according to motif to which the target genes are associated with. Bar height indicates significance of functional enrichment as it represents the $-\log_{10}(P\text{-Value})$ of functional enrichment in the given biological term or process as obtained from the DAVID Bioinformatic Resource (Database for Annotation, Visualization and Integrated Discovery) [19, 20] version 6.7, sponsored by the National Institute of Allergy and Infectious Disease (NIAID), NIH.
Figure S3: Correlation between motif activities and mRNA expression of cognate transcription factors. (a) Heatmap of the Pearson correlation coefficients (PCC) between the motif activities and mRNA expression profiles of associated TFs for a selection of TFs specifically dysregulated in promoted tumors. Each column corresponds to one of the 4 experimental data-sets (black = kinetic study, green = β-catenin KO study, red = CAR KO study and blue = tumor study) and PCC is indicated by color running from −1 (green), to 1 (purple). PCCs close to zero are colored white. (b) Scatter plots of motif activities against mRNA expression of associated TFs for a selection of 4 TFs. Each column of panels corresponds to one TF and each row of panels corresponds to one of the 4 experimental data-sets.

Figure S4: Alpha fetoprotein (Afp) gene expression in liver samples from 13 week kinetic data-sets as a surrogate gene of post-natal liver development termination. Gene expression is given as mean ±SD (n=3-5 animals per group). Open bars = control. Black bars = phenobarbital-treated samples.
Figure S5: Gene Ontology and KEGG enrichment analysis of predicted targets for motifs underlying early PB-mediated transcriptional dynamics. (a-d) Plots of the activity profiles of the first four right singular vectors. (e)-(l) Selection of biological pathways and functional categories (Gene Ontology or KEGG) enriched among target genes of motifs that contribute/correlate negatively (e-h) or positively (i-l) to each of the singular vectors. Each color corresponds to one regulatory motif, indicated at the bottom of each panel, and the size of each bar corresponds to the significance ($-\log_{10}(p\text{-value})$) of the enrichment.
Figure S6: Singular Value Decomposition analysis of the activity matrix of the CAR KO data-set. (a) Proportion of variance of the motif activity matrix. The first (blue bar) and second (green bar) components account for 33% and 18% respectively of the variance. (b) Barplot of the activity of the first two right singular vectors v1 and v2 in corresponding samples. White bars indicate activities for the control samples and black bars activities for the PB-treated samples. (c) Scatter plot of the correlations $\rho_i$ and projections $\pi_i$ of all motifs $i$ with the first and second right singular vectors respectively. Grey and black dots depict negatively and positively selected motifs.
Figure S7: Singular Value Decomposition analysis of the activity matrix of the tumor data-set. (a) Proportion of the variance of the motif activity matrix captured by the first singular vectors. The first (blue bar) and second (green bar) components account for 32% and 25% respectively of the variance. (b) Barplot of the activity of the first two right singular vectors v1 and v2 across the corresponding samples. White bars indicate activities for the normal samples and black bars activities for the tumor samples. (c) Scatter plot of the correlations $\rho_i$ and projections $p_i$ of all motifs $i$ with the first and second right singular vectors respectively. Grey and black dots depict negatively and positively selected motifs.
4 Abbreviations contained in Tables S1-S5

Tables S1-S5 contain motifs corresponding to specific groups that are

1. Table S1 - motifs associated with the first four singular vectors obtained from singular value decomposition (SVD) of the inferred motifs activity matrix from early kinetic study

2. Table S2 - motifs down-stream of CAR signaling

3. Table S3 - motifs dysregulated in both promoted and non-promoted tumors

4. Table S4 - motifs specifically dysregulated in promoted tumors

5. Table S5 - motifs down-stream of β-catenin signaling.

They are all formatted in the same way and their abbreviations are described in the following:

1. Representative motifs associated with the first four singular vectors obtained from SVD of the inferred motifs activity matrix from early kinetic study

   \( \text{PC1} = \) first singular vector associated with liver maturation

   \( \text{PC2} = \) second singular vector associated with constant xenobiotic response

   \( \text{PC3} = \) third singular vector associated with transient mitogenic response

   \( \text{PC4} = \) fourth singular vector associated with progressive xenobiotic response

   + = motifs correlating positively with corresponding singular vector

   - = motifs correlating negatively with corresponding singular vector

2. Z-value of motif significance that quantifies the significance of each motif in explaining the observed gene expression variation across the samples in the specified data-set

   \( S1 = \) kinetic data-set

   \( S2 = \) β-catenin KO data-set

   \( S3 = \) CAR KO data-set

   \( S4 = \) tumor data-set.

3. Z-values of differential motif activity that quantifies the evidence for a different regulatory activity of the motif between the two following conditions

   \( d_i = \) PB-treated and control samples at corresponding time-point

   \( KO = \) knock-out and wild-type samples

   \( PB, \text{wt} = \) PB-treated and non-treated wild-type samples of the KO data-sets

   \( PB, \text{ko} = \) PB-treated and non-treated KO samples of the KO data-sets

   \( \beta\text{-catenin} = \) promoted tumors and treated surrounding normal tissue

   \( \text{H-ras} = \) non-promoted tumors and surrounding non-treated normal tissue.

5 Supplementary Tables
Table S1: Representative motifs of the first four singular vectors (explaining over 70% of the variance in the activity matrix) obtained from singular value decomposition of the inferred motifs activity matrix from early kinetic study and underlying the early dysregulated biological pathways. Z-values of differential activity were computed as explained in Materials and Methods section of the main manuscript.
Table S2: Motifs which activities are significantly changing either 1) upon CAR KO in non-treated samples, 2) only in CAR wild-type samples and thus potentially down-stream of CAR signaling under physiological condition, or under PB treatment 2) and thus potentially down-stream of CAR signaling under PB treatment, or 3) only in CAR KO samples. Z-values of differential activity were computed as explained in Material and Method section of the main manuscript.

| Representative motifs | Motif Significance [z-value] | Kinetic study | Differential Motif Activity | CAR study | Tumor study |
|-----------------------|-----------------------------|---------------|-----------------------------|-----------|------------|
|                       |                            | d1    | d3  | d7  | d14 | d28 | d57 | d91 | KO | PB, wt | PB, ko |
| JUN, FOS, JUNB, FOSB  |                            | -0.3  | 1.8 | 1.1 | 0.0 | 0.2 | 2.7 | 2.1 | -1.3 | 1.7 | 2.6    |
| NFKB1, REL, RELA      |                            | 0.5   | 1.7 | 1.2 | 1.3 | 1.2 | 0.7 | 1.8 | -0.7 | 0.3 | 0.4    |
| NKX3-2                |                            | 0.8   | 0.9 | 0.4 | 0.5 | 1.0 | 0.2 | 1.8 | 2.1 | -0.5 | 2.8    |
| ONECUT1,2             |                            | -1.4  | -0.7 | -1.0 | -0.8 | -1.4 | -1.6 | -1.6 | -0.6 | 0.2 | 0.6    |
| NKX2-2,8              |                            | -0.1  | 0.5 | 0.2 | 0.1 | 0.9 | 1.7 | 1.6 | -1.3 | 0.9 | 0.9    |
| ZNF143                |                            | 2.7   | 2.2 | 0.3 | 0.4 | 0.9 | 0.2 | 1.8 | 0.6 | 0.4 | 0.3    |

Motifs down-stream of CAR signaling under physiological condition

| Motifs down-stream of CAR signaling under PB treatment |
|-------------------------------------------------------|
| FOX, FOS, JUNB, FOSB                                 |
| NFKB1, REL, RELA                                     |
| NKX3-2                                               |
| NKX2-2,8                                             |
| REST                                                 |
| IRF1,2,7                                             |
| LMO2                                                 |
| FOSL2                                                |
| RNF4,3,4                                             |
| HOX3,4                                               |
| GLI3                                                 |
| NFY, A, B, C                                         |
| AHR, ARNT, ARNT2                                     |
| CREB1                                                |
| ELF1,2,4                                             |
| ELK3,4, GABP(A, B)                                   |
| ZNF143                                               |
| NRF1                                                 |
| FOXD3                                                |

Motifs differentially active upon PB treatment only in KO

| Motifs differentially active upon PB treatment only in KO |
|----------------------------------------------------------|
| SFH, ZNF14                                               |
| NFKB1, REL, RELA                                         |
| NKX3-2,8                                                |
| HOX3,4,5                                                |
| NIRF1                                                  |
| FOSL2                                                  |
| RNF4,3,4,4                                              |
| HOX3,4                                                  |
| GLI3                                                   |
| NFY, A, B, C                                            |
| AHR, ARNT, ARNT2                                        |
| CREB1                                                  |
| ELF1,2,4                                                |
| ELK3,4, GABP(A, B)                                      |
| ZNF143                                                 |
| NRF1                                                   |
| FOXD3                                                  |

Motifs which activities are significantly changing either 1) upon CAR KO in non-treated samples, 2) only in CAR wild-type samples and thus potentially down-stream of CAR signaling under physiological condition, or under PB treatment, or 3) only in CAR KO samples. Z-values of differential activity were computed as explained in Material and Method section of the main manuscript.
### Table S3: Motifs which activities are significantly changing in promoted tumors relative to surrounding normal tissue, and in non-promoted tumors relative to surrounding non-treated normal tissue. These motifs are thus candidate regulators of liver tumorigenesis. Z-values of differential activity were computed as explained in the Material and Method section of the main manuscript.

| Representative motifs | Motif Significance | Kinetic study | Differential Motif Activity |
|-----------------------|--------------------|---------------|-----------------------------|
|                       | [z-value]          | d1  d3  d7  d14  d28  d57  d91  b-catenin study | b-catenin PB pb  PB ko  CAR study  Tumor study |
| TFAP2(A.C)            | +                  | -1.8 -1.9 -1.1 -1.3 -1.4 -4.0 | 1.0  KO KO PB pbPB ko -1.6 -3.7 |
| NR6A1                 | 1.4 0.8 1.0 2.0 | -0.4 0.9 -1.2 -0.1 -2.0 | -1.2 0.3 -1.0 -0.7 -2.0 -3.5 |
| TCF4-dimer            | -                  | 0.1 0.4 0.5 0.0 -0.1 -2.1 -1.9 | -1.5 -0.1 -0.2 -0.2 -1.9 -3.2 |
| GATA6                 | 0.9 0.8 1.0 1.7 | -0.5 0.2 0.9 -0.4 -0.1 -1.4 -0.3 | -0.9 0.5 0.1 -0.5 -2.7 -2.3 |
| NR5A1.2               | +                  | 0.8 -0.1 0.4 0.4 0.5 -2.6 | 1.9 17 -0.5 -18 -2.8 -2.0 |
| NR1H1                 | 1.7 0.2 1.8 2.8 | -1.4 -1.4 -0.2 -0.2 -0.1 -1.6 | 0.0 0.9 0.1 -0.8 -4.7 -1.7 |
| SOX(89,10)            | 1.0 0.6 1.0 1.6 | -1.0 -0.7 0.1 -0.1 -1.2 0.7 -1.8 | 0.6 -0.8 -0.2 0.6 2.0 2.5 |
Table S4: Motifs which activities are significantly changing in promoted tumors relative to surrounding treated normal tissue, but not in non-promoted tumors relative to surrounding non-treated normal tissue. These motifs are thus candidate regulators of tumor promotion. Z-values of differential activity were computed as explained in Material and Method section of the main manuscript.
Table S5: Motifs which activities are significantly changing upon 
\( \beta \)-catenin KO in non-treated samples and thus potentially down-stream of \( \beta \)-catenin signaling under physiological condition. *Z*-values of differential activity were computed as explained in Material and Method section of the main manuscript.

| Representative motifs | Motif Significance \[z\text{-value}\] | Kinetic study | Differential Motif Activity | \( \beta \)-catenin \[KO\] study | \( \beta \)-catenin \[KO\] study |
|----------------------|--------------------------------------|------------------|-----------------------------|--------------------------------|--------------------------------|
| **TCE**              |                                      |                  |                             |                                |                                |
| ESR1                 | +                                    | -2.8             | 0.7                         | -0.1                           | 0.0                            |
| **PIK3**             |                                      |                  |                             |                                |                                |
| E2F                  |                                      |                  |                             |                                |                                |
| **PAX**              |                                      |                  |                             |                                |                                |
| **POU**              |                                      |                  |                             |                                |                                |
| **GATA**             |                                      |                  |                             |                                |                                |
| **FOX**              |                                      |                  |                             |                                |                                |
| **SPI**              |                                      |                  |                             |                                |                                |

Note: \( \beta \)-catenin KO in non-treated samples and thus potentially down-stream of \( \beta \)-catenin signaling under physiological condition. *Z*-values of differential activity were computed as explained in Material and Method section of the main manuscript.
| Affx | GS | Motifs | Pearson study | *P*-value | Manufacturers study | *P*-value | EAM Kit study | *P*-value | Tumor Study | *P*-value |
|------|----|--------|---------------|-----------|---------------------|-----------|---------------|-----------|-------------|-----------|
| 142070_at | Ahr | AHR,ARNT,ARNT2 | 0.07 | 1.0E-01 | 0.01 | 2.67E-01 | 0.13 | 9.8E-01 | 0.14 | 9.8E-01 |
| 141071_at | Ahr | AHR,ARNT,ARNT2 | 0.08 | 1.0E-01 | 0.01 | 2.67E-01 | 0.13 | 9.8E-01 | 0.14 | 9.8E-01 |
| 142070_at | Ahr | AHR,ARNT,ARNT2 | 0.07 | 1.0E-01 | 0.01 | 2.67E-01 | 0.13 | 9.8E-01 | 0.14 | 9.8E-01 |
| 141071_at | Ahr | AHR,ARNT,ARNT2 | 0.08 | 1.0E-01 | 0.01 | 2.67E-01 | 0.13 | 9.8E-01 | 0.14 | 9.8E-01 |
| 141052_at | Ahr | AHR,ARNT,ARNT2 | 0.07 | 1.0E-01 | 0.01 | 2.67E-01 | 0.13 | 9.8E-01 | 0.14 | 9.8E-01 |
| 141071_at | Ahr | AHR,ARNT,ARNT2 | 0.08 | 1.0E-01 | 0.01 | 2.67E-01 | 0.13 | 9.8E-01 | 0.14 | 9.8E-01 |
| 141052_at | Ahr | AHR,ARNT,ARNT2 | 0.07 | 1.0E-01 | 0.01 | 2.67E-01 | 0.13 | 9.8E-01 | 0.14 | 9.8E-01 |
| 141071_at | Ahr | AHR,ARNT,ARNT2 | 0.08 | 1.0E-01 | 0.01 | 2.67E-01 | 0.13 | 9.8E-01 | 0.14 | 9.8E-01 |

**Table S6:** Pearson correlation coefficient (PCC) and associate *P*-values between motif activities and mRNA expression of cognate transcription factors in each data-sets - part 1. Part 2 in Table S7. Affx = probe-set ID from Affymetrix platform Mouse 430.2. GS = gene symbol. PCC = Pearson correlation coefficient.
| Affx   | GS | Motifs     | Kinetic study PCC | Kinetic study P-value | Orthostatic study PCC | Orthostatic study P-value | CAB KO study PCC | CAB KO study P-value | Transl Study PCC | Transl Study P-value |
|--------|----|------------|-------------------|-----------------------|-----------------------|--------------------------|-------------------|---------------------|-----------------|---------------------|
| 141475_s_at | Lhx4 | LHX4 /PAX5 /ZBTB16,2 | 0.89 | 4.3E-01 | 0.69 | 4.1E-01 | 0.34 | 1.3E-01 | 0.34 | 1.3E-01 |
| 141475_s_at | Lhx4 | LHX4 /PAX5 /ZBTB16,2 | 0.89 | 4.3E-01 | 0.69 | 4.1E-01 | 0.34 | 1.3E-01 | 0.34 | 1.3E-01 |
| 141475_s_at | Lhx4 | LHX4 /PAX5 /ZBTB16,2 | 0.89 | 4.3E-01 | 0.69 | 4.1E-01 | 0.34 | 1.3E-01 | 0.34 | 1.3E-01 |
| 141475_s_at | Lhx4 | LHX4 /PAX5 /ZBTB16,2 | 0.89 | 4.3E-01 | 0.69 | 4.1E-01 | 0.34 | 1.3E-01 | 0.34 | 1.3E-01 |
| 141475_s_at | Lhx4 | LHX4 /PAX5 /ZBTB16,2 | 0.89 | 4.3E-01 | 0.69 | 4.1E-01 | 0.34 | 1.3E-01 | 0.34 | 1.3E-01 |
| 141475_s_at | Lhx4 | LHX4 /PAX5 /ZBTB16,2 | 0.89 | 4.3E-01 | 0.69 | 4.1E-01 | 0.34 | 1.3E-01 | 0.34 | 1.3E-01 |
| 141475_s_at | Lhx4 | LHX4 /PAX5 /ZBTB16,2 | 0.89 | 4.3E-01 | 0.69 | 4.1E-01 | 0.34 | 1.3E-01 | 0.34 | 1.3E-01 |
| 141475_s_at | Lhx4 | LHX4 /PAX5 /ZBTB16,2 | 0.89 | 4.3E-01 | 0.69 | 4.1E-01 | 0.34 | 1.3E-01 | 0.34 | 1.3E-01 |
| 141548_s_at | Gata1 | GATA1 | 0.61 | 7.6E-01 | 0.61 | 8.2E-01 | 0.01 | 9.5E-01 | 0.99 | 1.1E-01 |
| 142077_s_at | Mdm2 | MDM2 | 0.32 | 3.4E-01 | 0.24 | 4.0E-01 | 0.16 | 2.4E-01 | 0.16 | 2.4E-01 |
| 142213_s_at | Nkx2-2 | Nkx2-2,8 | 0.63 | 3.2E-04 | 0.38 | 1.8E-01 | 0.06 | 4.7E-01 | 0.06 | 4.7E-01 |
| 142325_s_at | Nfkb1 | NFKB1,REL,RELA | 0.81 | 3.1E-01 | 0.76 | 3.7E-01 | 0.71 | 3.1E-01 | 0.71 | 3.1E-01 |
| 142974_s_at | Nkx2-2 | Nkx2-2,8 | 0.67 | 1.4E-01 | 0.27 | 6.3E-01 | 0.45 | 9.5E-01 | 0.45 | 9.5E-01 |
| 142319_s_at | Nkx2-2 | Nkx2-2,8 | 0.67 | 1.4E-01 | 0.27 | 6.3E-01 | 0.45 | 9.5E-01 | 0.45 | 9.5E-01 |
| 142803_s_at | Nkx2-2 | Nkx2-2,8 | 0.67 | 1.4E-01 | 0.27 | 6.3E-01 | 0.45 | 9.5E-01 | 0.45 | 9.5E-01 |
| 142803_s_at | Nkx2-2 | Nkx2-2,8 | 0.67 | 1.4E-01 | 0.27 | 6.3E-01 | 0.45 | 9.5E-01 | 0.45 | 9.5E-01 |

Table S7: Pearson correlation coefficient (PCC) and associate P-values between motif activities and mRNA expression of cognate transcription factors in each data-sets - part 2. Affx = probe-set ID from Affymetrix platform Mouse 430_2. GS = gene symbol. PCC = Pearson correlation coefficient.
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