Supplementary Figures

Integrative Multi-Omics Flux Analysis Reveals Metabolic Mechanisms of Isoniazid-Induced Liver Toxicity

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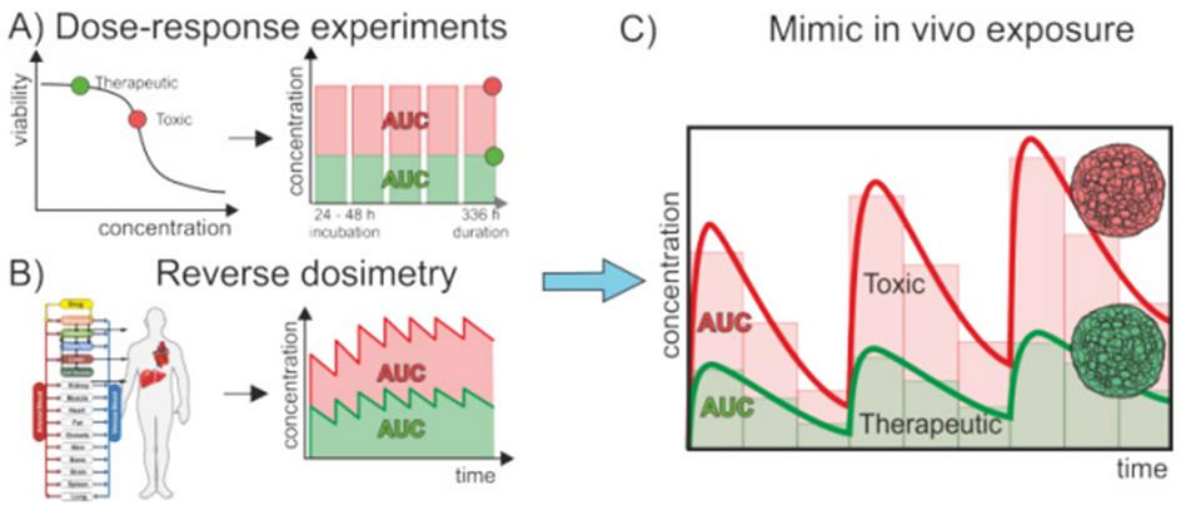
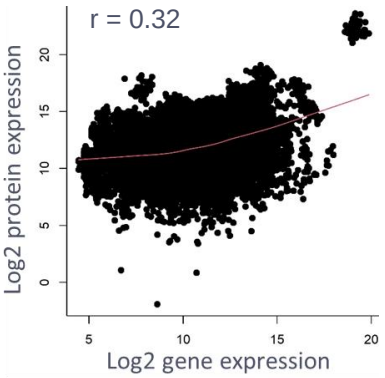
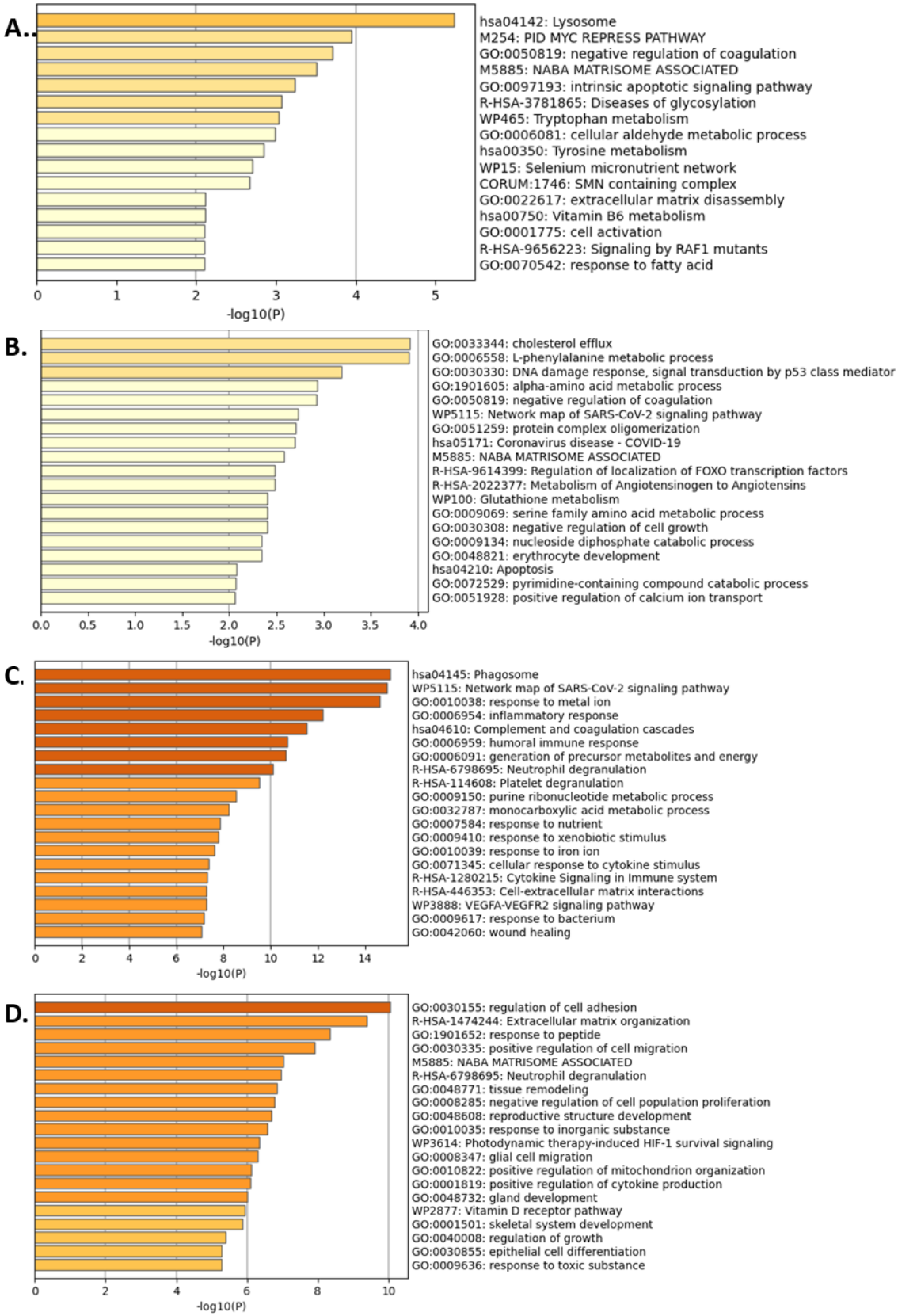


Supplementary Figure 1. BPK-based assay setup and reverse dosimetry

In vitro assay design to mimic organ-specific in vivo drug exposure. **A.** Dose–response experiments in human liver microtissues to identify a toxic exposure causing 20% reduction in cell viability. **B.** PBPK-based reverse dosimetry to estimate the in vivo daily dose producing equivalent hepatic exposure. **C.** Translation of continuous PBPK exposure profiles into an experimental dosing regimen with three daily media changes.

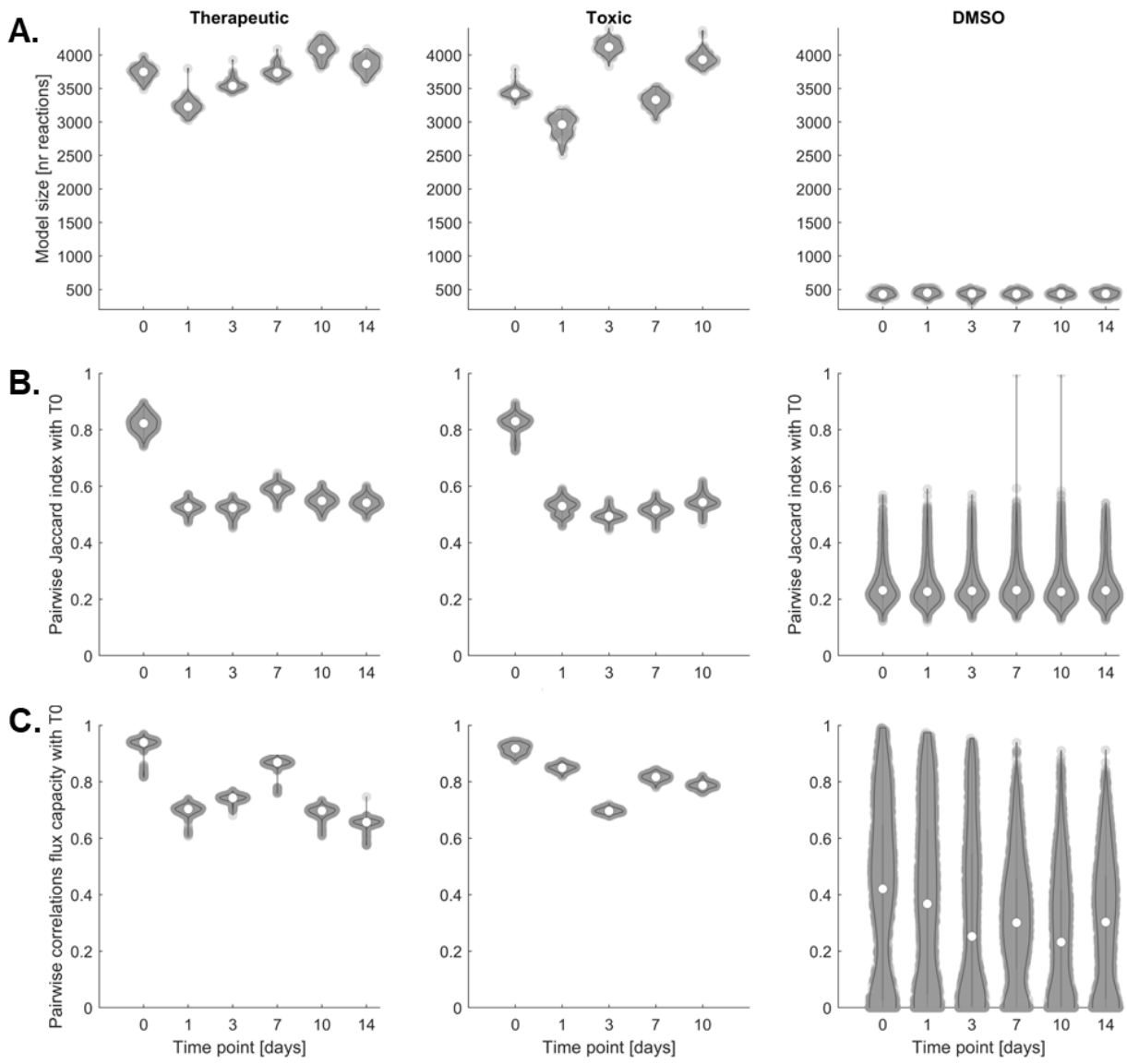


Supplementary figure 2. Scatterplot of log2-transformed protein vs. gene expression across all samples. Pearson correlation coefficient r = 0.32.

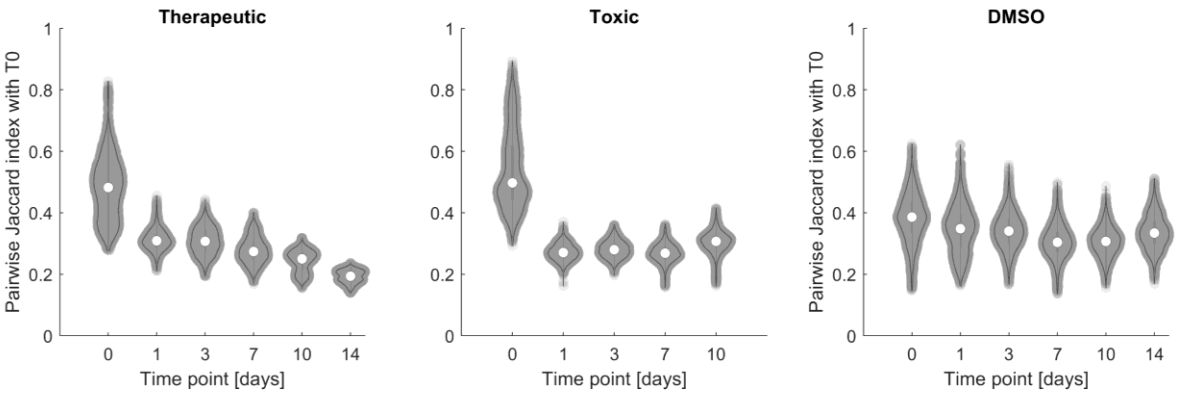


Supplementary Figure 3. Metascape enrichment analysis

Top 20 enriched terms identified by Metascape. **A.** Differentially expressed proteins (DEPs) under therapeutic exposure. **B.** DEPs under toxic exposure. **C.** Differentially expressed genes (DEGs) under therapeutic exposure. **D.** DEGs under toxic exposure.

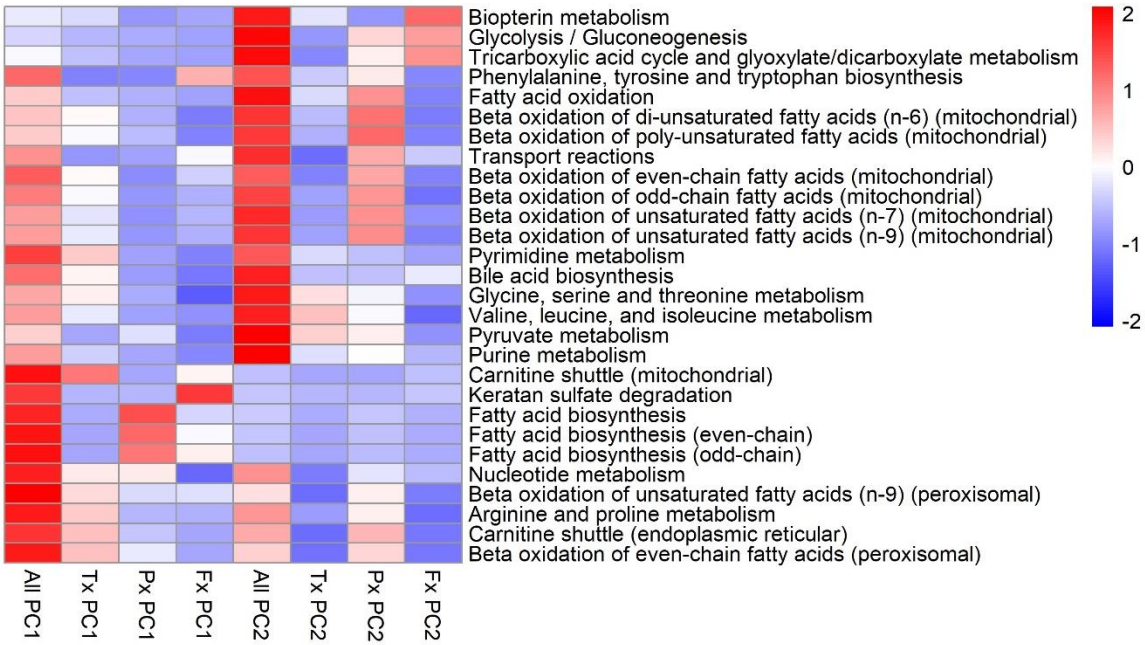


Supplementary Fig. 4. Context- specific models inferred from transcriptomics. Context-specific models inferred from transcriptomics and metabolic constraints for therapeutic, toxic, and DMSO control conditions. Each dot represents one of 100 alternative optimal model reconstructions. **A.** Model size (number of active reactions). **B.** Pairwise Jaccard index relative to T0 **C.** Pairwise Pearson correlation coefficients of flux capacities relative to T0.



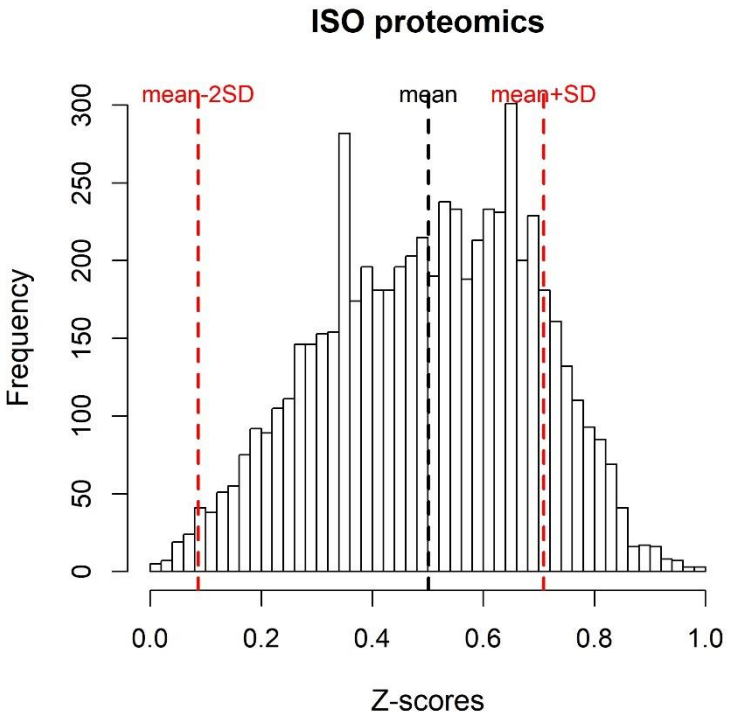
Supplementary Figure 5. Context- specific models inferred from proteomics.

Pairwise Jaccard index relative to T0 for context-specific models inferred from proteomics and metabolic constraints for therapeutic, toxic, and DMSO control conditions. Each dot represents one of 100 alternative optimal model reconstructions.



Supplementary figure 6. Integrated PCA analysis.

Pathway-level contributions to PC1 and PC2 per data layer (transcriptomics Tx, proteomics Px, fluxomics Fx), as well as their summed contribution. Pathway contributions are normalized by layer contribution; color scaling is relative to the mean contribution of each pathway.



Supplementary Fig. 7. Cut-off selection for context-specific models.

Reactions associated with expression above the mean plus one standard deviation were considered active, whereas reactions below the mean minus two standard deviations were considered inactive.