Creating and improving detoxification pathways for interpretation of toxicogenomics data

P. Giesbertz[1,2], J. Hummel[1,2], S. Gaj[1,2,3], D. Jennen[1,2], T. Kelder[3], C. Evelo[1,3], J. van Delft[1,2], J. Kleinjans[1,2]

1. Netherlands Toxicogenomics Centre, Maastricht University, The Netherlands
2. Dept. of Health Risk Analysis and Toxicology, Maastricht University, The Netherlands
3. Dept. of Bioinformatics – BiGCaT, Maastricht University, The Netherlands

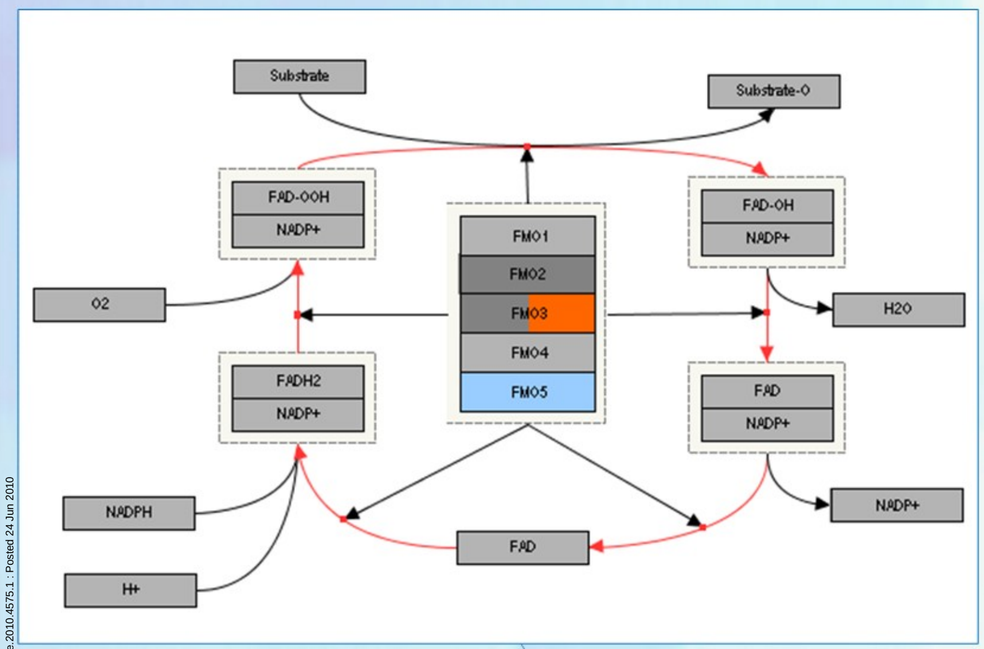
Introduction

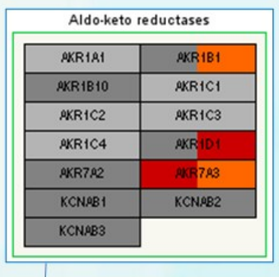
Current advances in high-throughput ~omics yield a large amount of biological data which needs to be interpreted in a correct manner. Biological pathways can be supportive in this interpretation by representing the data in an abstract way and combining them with our current biological knowledge. This project was intended to create pathways for toxicological research using WikiPathways [1]. Our focus was to create compound-specific and general biotransformation pathways. Furthermore, expression data from Iconix Biosciences [2] was used to observe the effect of Tamoxifen and Aflatoxin B1 on the detoxification process.

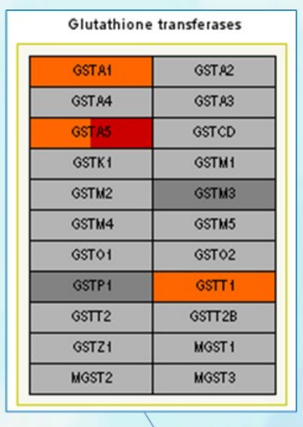
Results

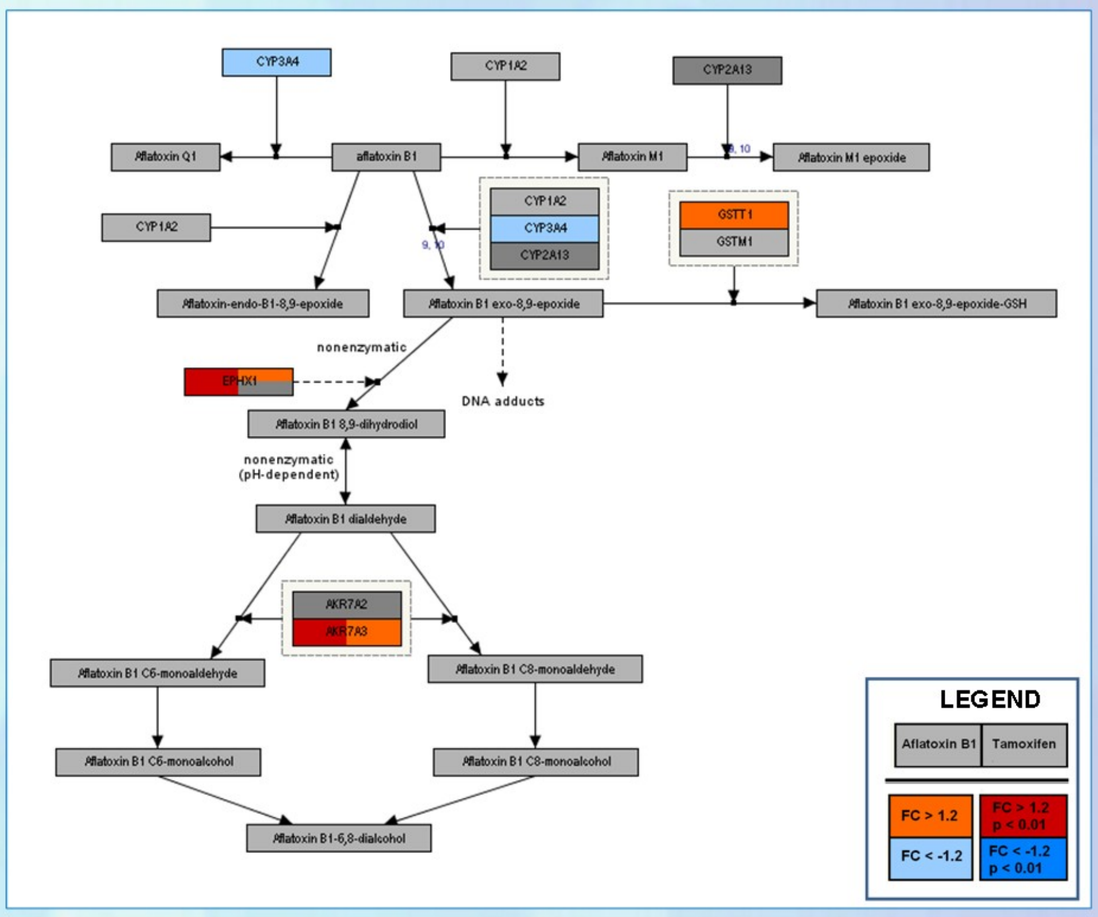
Tamoxifen and Aflatoxin B1 are differently metabolized by various liver enzymes and as such, are expected to have a different gene expression profile.

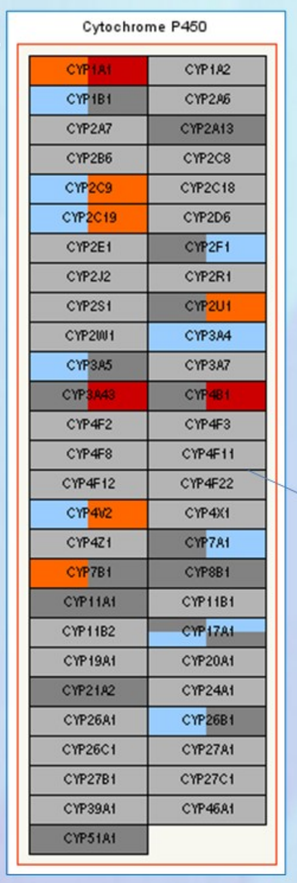
For genes involved in detoxification, a noticeable difference in the gene expression profile for both compounds was observed: Tamoxifen exposure causes an up-regulation of FMO3, which is an important factor in the phase I biotransformation of Tamoxifen. Regarding AKR7A2 and 7A3, known to be involved in Aflatoxin B1 metabolism, Aflatoxin B1 causes significant up-regulation of AKR7A3 while the effect of Tamoxifen on these genes is less clear.

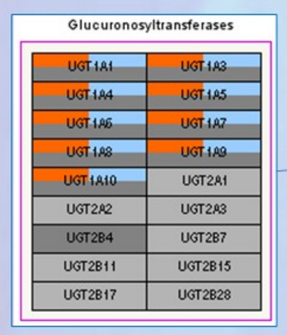


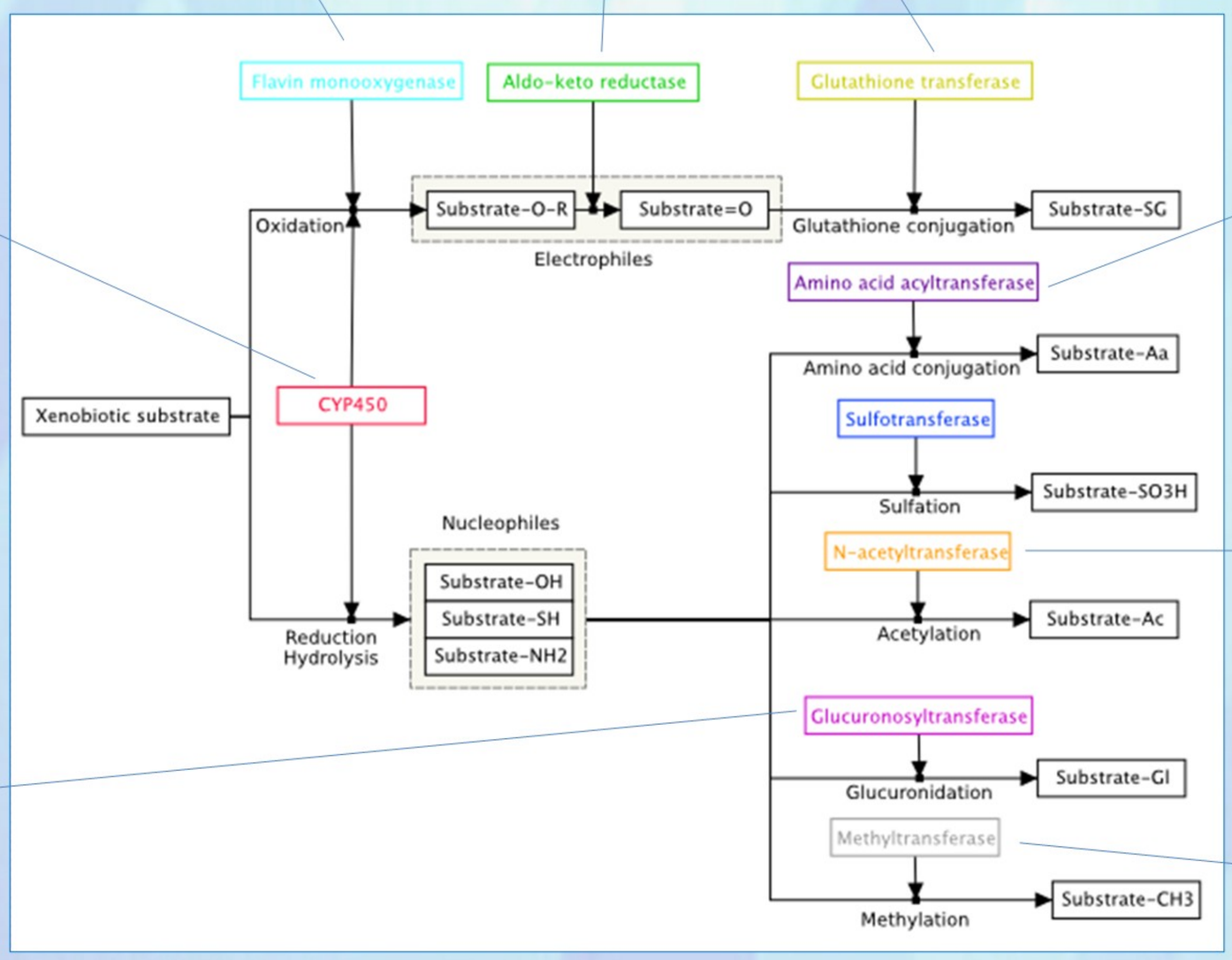


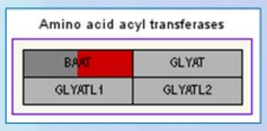


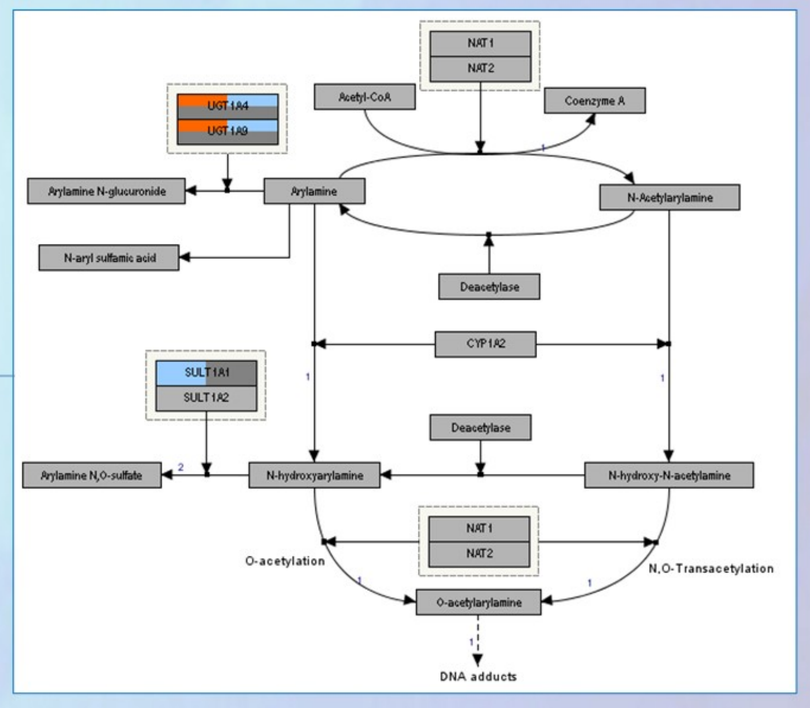


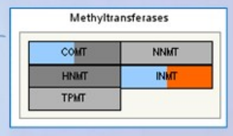












Methods

All pathway content was generated within WikiPathways using a combination of scientific literature and online resources such as Reactome. Microarray data coming from custom Rat GE Healthcare/Amersham Bioscience arrays were downloaded from Gene Expression Omnibus (GSE8858). Using R [3], subsets of Aflatoxin B1 (1 day; 0.3 mg/kg) and Tamoxifen (0.25 days; 64 mg/kg) exposure data were selected and seperately quantile normalized, followed by a few other data filtering steps. In the end, genes were considered to be differentially expressed when: 1) p-value < 0.01 and 2) |fold change| > 1.2. In a final step, Pathvisio was used to visualize these genes on the new toxicological pathways. The genes in the pathways consist of Aflatoxin B1 and Tamoxifen expression data at the left and the right part of the gene box, respectively.

References

1. Pico AR, et al. (2008) WikiPathways: Pathway Editing for the People. PLoS Biol 6(7)
2. Natsoulis G, et al. (2008) The liver pharmacological and xenobiotic gene response repertoire . Mol Syst Biol. 2008; 4:175
3. www.r-project.org

Correspondence:
Danyel.Jennen@GRAT.unimaas.nl