Detect Liver Toxicity through Causal Biological Network Model and Computational Algorithm.

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With the progression of omics technologies, we have developed Causal Biological Network Models that use high-throughput data to predict early toxicity [1-3]. Previously developed network models, focused on pulmonary and cardiovascular disease, demonstrated the relevance of the network approach in the quantification of the impact of exposures on biological processes. [4, 5]. Recently we have focused on modelling the xenobiotic metabolism process that results in the elimination of chemical or xenobiotic substances (i.e. compounds foreign to the body) [6, 7]. The enzymes involved in this process convert xenobiotics into hydrophilic derivatives that are then eliminated through excretion into the aqueous compartments of the tissues. Since the liver is the primary site of xenobiotic metabolism in mammals, we built a new suite of network models that represent biotransformation and chemical elimination involved in Phase I, Phase II and Phase III xenobiotic metabolism in the liver.

Nuclear receptors such as the aryl hydrocarbon receptor (AR), orphan nuclear receptors, and nuclear factor-erythroid two p45-related factor 2 (Nrf2) play a critical role in all phases of xenobiotic metabolism [6]. While Phase I and II xenobiotic metabolism network models largely describe the transformation of xenobiotic into hydrophilic product, Phase III model focuses on the xenobiotic transport and excretion. The combination of the network models with transcriptomics data and computational scoring algorithms could be a valuable approach for the pharmacological industry to predict early drug toxicity.

REFERENCES:

1. Martin F, Sewer A, Talikka M, Xiang Y, Hoeng J, Peitsch MC: **Quantification of biological network perturbations for mechanistic insight and diagnostics using two-layer causal models**. *BMC bioinformatics* 2014, **15**:238.
2. Martin F, Thomson TM, Sewer A, Drubin DA, Mathis C, Weisensee D, Pratt D, Hoeng J, Peitsch MC: **Assessment of network perturbation amplitudes by applying high-throughput data to causal biological networks**. *BMC systems biology* 2012, **6**:54.
3. Thomson TM, Sewer A, Martin F, Belcastro V, Frushour BP, Gebel S, Park J, Schlage WK, Talikka M, Vasilyev DM *et al*: **Quantitative assessment of biological impact using transcriptomic data and mechanistic network models**. *Toxicology and applied pharmacology* 2013, **272**(3):863-878.
4. Schlage WK, Westra JW, Gebel S, Catlett NL, Mathis C, Frushour BP, Hengstermann A, Van Hooser A, Poussin C, Wong B *et al*: **A computable cellular stress network model for non-diseased pulmonary and cardiovascular tissue**. *BMC systems biology* 2011, **5**:168.
5. Westra JW, Schlage WK, Frushour BP, Gebel S, Catlett NL, Han W, Eddy SF, Hengstermann A, Matthews AL, Mathis C *et al*: **Construction of a computable cell proliferation network focused on non-diseased lung cells**. *BMC systems biology* 2011, **5**:105.
6. Xu C, Li CY, Kong AN: **Induction of phase I, II and III drug metabolism/transport by xenobiotics**. *Archives of pharmacal research* 2005, **28**(3):249-268.
7. Nakata K, Tanaka Y, Nakano T, Adachi T, Tanaka H, Kaminuma T, Ishikawa T: **Nuclear receptor-mediated transcriptional regulation in Phase I, II, and III xenobiotic metabolizing systems**. *Drug metabolism and pharmacokinetics* 2006, **21**(6):437-457.