

Exploiting systems chemical biology to predict and understand (un)desired drug effects

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Several drug withdrawals associated with adverse side effects –Vioxx® and Lipobay® being the most prominent ones – gained broad attention in recent years. To avoid such cases and thereby improve the life of patients it is without question highly desirable to identify and eliminate such problems in early research.

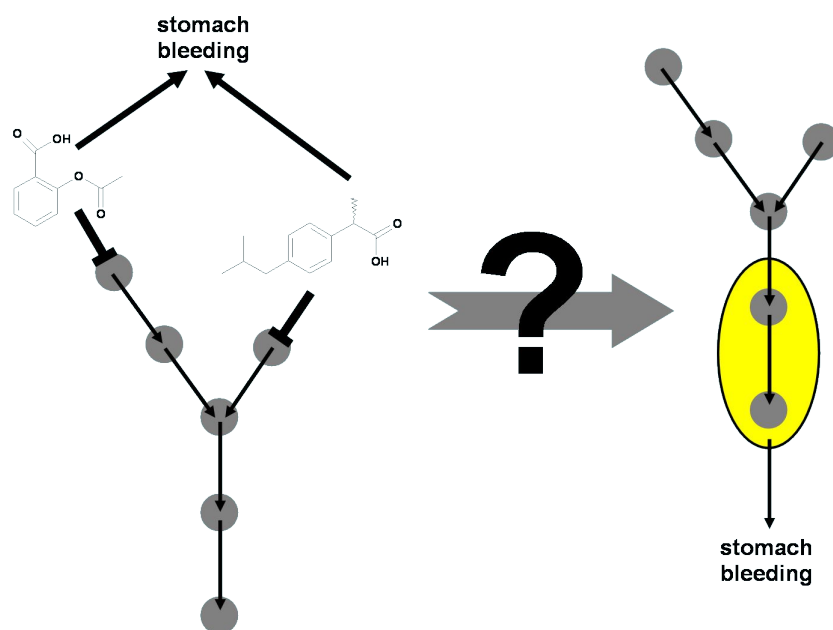


Figure 1: This figure illustrates that the interaction of a compound with a single target may not always be the isolated cause for an undesired effect. Hitting two different targets can have the same outcome downstream in a pathway. This contribution will deal with approaches to address such cases through the combination of cheminformatics approaches with systems biology data.

In some cases the reason for an undesired effect can be found in the interaction of the compound with a certain target, e.g. the prolonged QT-syndrome with the hERG-channel.¹ These cases can then be identified with well-established *in vitro*-methods,² as well as newly developed *in silico*-methods.³⁻⁵ However, often chemically diverse compounds cause similar problems. This is the case when two different targets are hit in the same biological pathway, which is illustrated for stomach bleeding in Figure 1. In this case models can be established that predict certain adverse effects irrespective of target considerations, where the models are based on compound-adverse event pairings. After computing these models a link through chemical space can be made to compute correlations with different target prediction models.³ Thereby it becomes possible to link certain phenotypic effects to the interaction between a molecule and a target.

This contribution will introduce an extension of these methods. On the one hand the predictive models for both adverse side effects and targets have been optimized, re-calculated and heavily validated using the MedDRA terminology for side effects⁶ and sophisticated validation methods.⁷ Further, we linked the predictions with biological network information to establish firm links between side effects and the interference of a compound with a certain pathway. The

predictions can then be validated by analyzing the data from well-known pathway tools and databases like GeneGo's MetaCore and Ingenuity's IPA. Also, new links between pathways and side effects can be established.

To summarize: The presentation will link Systems Chemical Biology⁸ approaches to the field of adverse side effects of drugs to better understand the latter ones.

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