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Commentary

Towards the network-based prediction of repurposed drugs using patient-specific metabolic models

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The high costs of novel drug development and financial risks linked to failures in clinical trials, has led pharmaceutical companies to search for new indications for already approved and well-studied drugs with known side effects. This process known as drug repurposing or drug repositioning accounted for 20% of all drugs released in 2013 in the US. In the recent years, metabolic modelling approaches have been successfully used to predict drug targets and drugs for repurposing [1] by simulating the effect of thousands of drugs on various cancer types while also predicting potential side effects [2].

The first metabolic models that have been used for drug repurposing were generic cancer models or generic disease models that integrated and combined data from different samples and cell lines. These consensus models allowed finding novel drug targets primarily in the central carbon system [1] that has been highly conserved across most cancer types or tumors of a same type.

Since then, the advent of very efficient model-building algorithms [3–5] and the increase of the reconstructed model's robustness and resolution power (capacity to capture metabolic variations between different conditions and contexts) enables to consider the reconstruction of personalised metabolic models for patients in order to predict tailored repositioned drug treatments [6].

The question remains to be answered whether building patient-specific or consensus cancer-type/generic models for drug response prediction is the optimal strategy. Both approaches have their caveats and advantages. In the article of *EBioMedicine* [7], Turanli and colleagues opted for the reconstruction of a consensus prostate cancer model from >450 personalised models because the patient-specific models showed a large variability in the number of reactions and associated genes, which might be explained by the inherent cancer heterogeneity. When talking about cancer heterogeneity, one distinguishes between inter-tumor and intra-tumor heterogeneity. *A priori,* the high inter-tumor heterogeneity advocates against the building of consensus models as many cancers such as breast, colorectal, and prostate cancer show different molecular subtypes based on the tumor mutation state that have a predictive factor in regard of therapeutics efficiency. Patient-stratification and model reconstruction based on patient or group-specific samples might be an appropriate strategy to find high efficiency drugs for the given patient group that might have only a low or no effect for other patient groups. For example, if a patient shows a specific tumor mutation, personalised models can be used to find novel drugs and drug targets that would have been missed otherwise and therefore could greatly benefitting the patients. Furthermore, generic models are more likely to predict already known drug targets while focussing on well-conserved and intensively studied reactions signatures. However, when considering the intra-tumor heterogeneity, which does not take into account the molecular subtyping or personalised models, finding more generic drugs that would have an effect on a wider spectrum of cancer cells could reduce the risk of selecting for resistant cancer clones. In addition, personalised models have a higher resolution power and, therefore, are more likely to unravel new drug targets but are less robust to noise than generic models.

Even though, metabolic modelling has been successfully used to discover new drug targets while the model quality has greatly improved over the last couple of years, there are some important challenges to keep in mind. First off, a context specific model is only as good as the original input model [8]. Most input models should be qualified as a reconstruction rather than a model. Models can be readily used for modelling purposes and can be obtained from a global reconstruction whose attempt it is to be as complete as possible in terms of known reactions, genes, and metabolites. Because reconstructions incorporate many reaction that are not simultaneously active in a cell, they are prone to the existence of loops [9] that would hinder downstream analysis.

Moreover, the accuracy, resolution power, and noise robustness of a metabolic model is highly variable and strongly depended on the context-specific model building algorithm as well as on data preprocessing and integration [10].

Although, personalised models can capture the intra-tumor heterogeneity, the high inter-model variance can, to some extent, be explained by the bias introduced from the context-specific model-building algorithm used, batch effects, or the setting of arbitrary thresholds during data integration. While metabolic modelling and personalised models have the potential to be routinely used by pharmaceutical companies for drug discovery and drug repurposing, more throughout and systematic benchmarking of context-specific models, algorithms as well as the prepossessing and integration workflow of proteomic and transcriptomic data into genome-scale metabolic reconstructions will

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be required in order to increase the robustness and accuracy of these models.

Taken together, the work of Turanli and colleagues [7] describes an innovative workflow for the integration of proteomic and transcriptomic data that allows dealing with the high heterogeneity in cancer. By using a consensus model as canvas for the integration of differentially expressed genes, reporter metabolites, and drug signatures obtained from CMap2, drugs that could potentially reverse the gene expression in prostate cancer have been predicted. One of the predicted drugs, Ifenprodil, was shown to inhibit the growth of a prostate cancer cell line *in vitro*.

Disclosure

The authors declared no competing interests.

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