QP Hot-topic

USING A SYSTEMS PHARMACOLOGY APPROACH TO UNDERSTAND MECHANISMS OF ADVERSE DRUG REACTIONS OF IMMUNE CHECKPOINT INHIBITORS

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Challenges

After a long battle vindicating its effectiveness, immunotherapies have emerged as a key pillar in cancer therapy with the approvals of ipilimumab, nivolumab and pembrolizumab, inhibiting either cytotoxic T-lymphocyte antigen-4 (CTLA-4, ipilimumab) or programmed death-1 (PD-1, nivolumab & pembrolizumab)[1]. Yet, the battle with immunotherapies still confronts many challenges given the high variability in their exposure-response patterns and their safety profiles[2]. Sources of this high variability lie within the genetics of cancer as well as in the heterogeneous inter- and intra-patient variability in tumor expression and in the response to therapies.

Back Translation using Adverse Drug Reaction (ADR) Reports

In order to contribute to the battle and the understanding of compromised efficacy as a result of off-target safety events seen with immunotherapies, we propose a systems pharmacology approach analyzing post-market surveillance data of adverse drug reaction (ADR) reports from the FDA Adverse Event Reporting System (FAERS)[3]. Using this systems approach, back translation from ADR reports to molecular pathways and target levels was investigated to generate a hypothesis regarding the underlying molecular mechanisms of the respective ADR.

The data analytical platform MH Effect™ was utilized to map the ADR reports from FAERS to chemical and biological databases, i.e. DrugBank, PubChem, UniProt, NCI-Nature, Reactome and BioCarta in order to generate target ADR profiles for each biomolecule in the databases via the integration of drug-target ADR data[4] (Figure 1). Disproportionality analysis, using the proportional reporting ratio (PRR)[5], was used to assess the statistical relevance between cohorts

and events of interest. Literature search was performed to compare the established hypotheses to experimental findings.

During this analysis certain limitations which come with FAERS data needed to be taken into account such as: i) few reported numbers of ADR events with immune checkpoint inhibitors given the short approval times, ii) no detailed information on concomitant use of multiple drugs such as the timing when co-medications were started or stopped during the treatment cycle, and iii) FAERS data can have misstatements of indications, ADRs, or co-administered medications[4].

Case Study

We investigated how mechanistic differences between CTLA-4 and PD-1, which are negative regulators of T-cell activation, affect colitis, one of the major ADRs of immunotherapies (Figure 2). Using the proposed systems-based approach, we verified that ipilimumab is associated with a higher PRR and a larger number of ADR reports with colitis than those of nivolumab & pembrolizumab. By comparing PRRs of inflammatory signalling mechanisms, we found that ipilimumab is more involved in the signaling pathways of inflammatory cytokines than nivolumab & pembrolizumab. Lastly, we found that ipilimumab is more associated with an early stage of an immune response than nivolumab & pembrolizumab. Thus, we hypothesized that ipilimumab could induce a more severe rate of colitis than nivolumab & pembrolizumab due to a greater magnitude of T-cell activation as a result of earlier response of ipilimumab in the immune response. This proposed hypothesis can inform future experimental and clinical investigational study designs during the development of immunotherapies.

Conclusion

This systems-based platform could be used to inform drug development pipelines by back translating from post-market surveillance safety reports to the molecular mechanisms and targets of ADR events. The hypothesized safety profile can be projected to a novel drug under development with similar molecular mechanism.

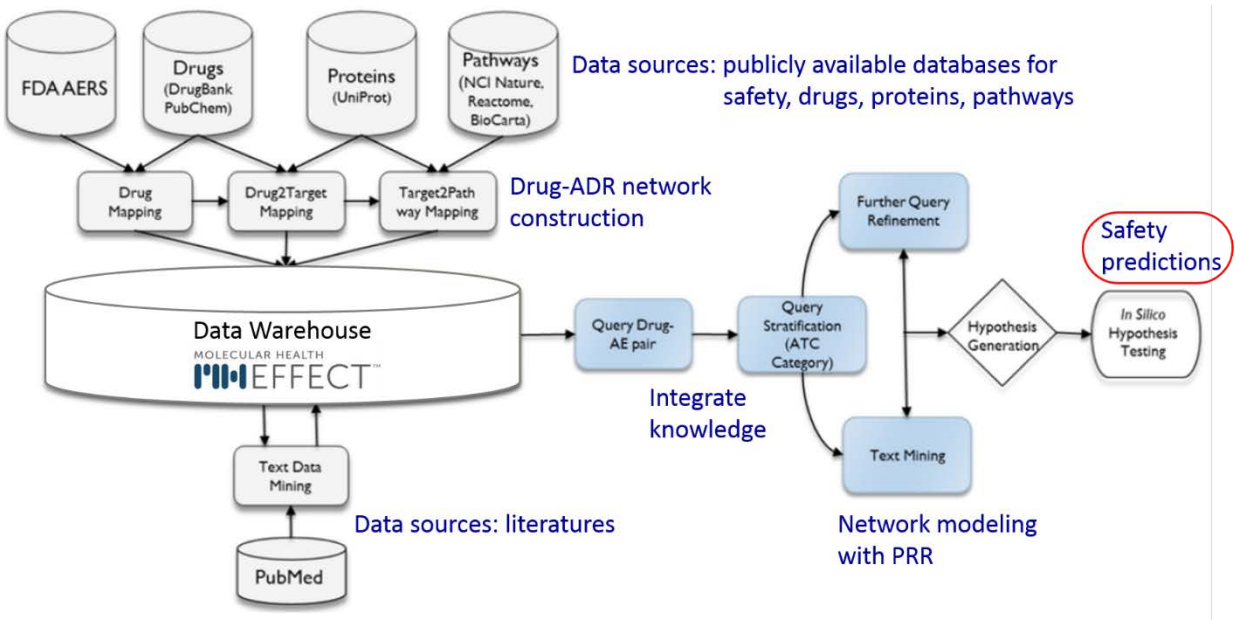

Figure 1. Overview of analysis workflow using MH Effect™. This figure was adapted from P. Schotland, *et al*. *Eur. J. Pharm. Sci.* **94**, 84–92 (2016).

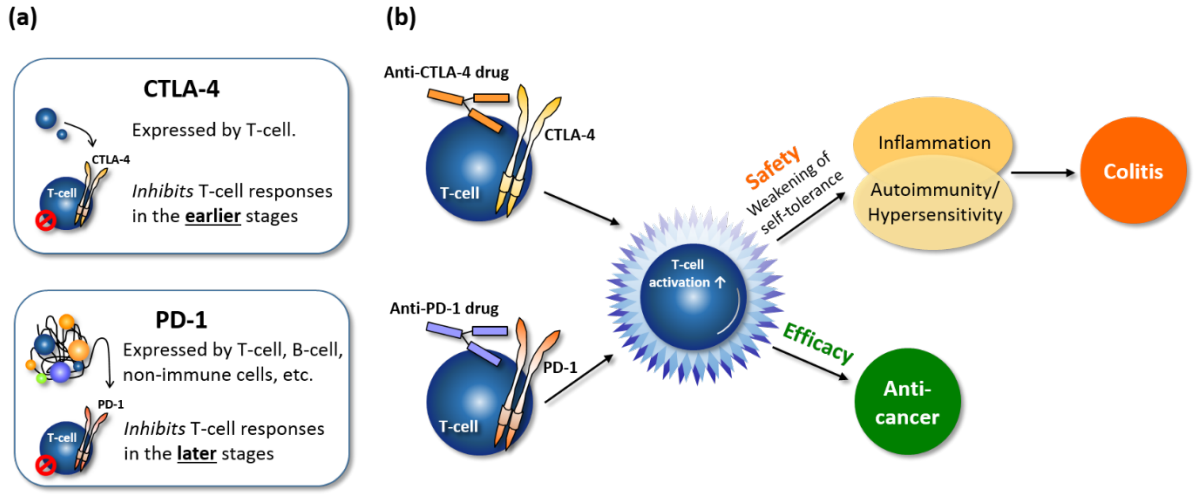

Figure 2. (a) Mechanistic differences between CTLA-4 and PD-1. (b) The immune-mediated toxicity, colitis, and the mechanism of action of the immune checkpoint inhibitors.

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For additional topic topics

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