A COLLABORATIVE VENTURE FOR DRUG TOXICITY PREDICTION

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The incident with the experimental fatty acid amide hydrolase (FAAH) inhibitor BIA 10-2474 during a clinical study in which one study participant died and five participants were hospitalized is nearly a year old [1]. The irreversible binding and limited specificity of BIA-10 2474 [1] make it a high-risk candidate for adverse events. Several reasons for these seemingly unexpected adverse drug effects have been previously suggested [2]. The endocannabinoid system (ECS) targeted by FAAH inhibitors has been studied for several pathophysiologies including chronic pain, appetite control, anxiety and the immune response, making it a promising but also challenging system to modulate therapeutically.

Another very recent example is a case report published in NEJM, which described the occurrence of rare but fatal adverse event due to acute heart failure with anti-cancer immune checkpoint inhibitors [3]. It is relatively easy to understand that suppressing immune check points will increase the probability of the immune system attacking native organs. However why does this not happen in everybody? The answers may lie in considering responses across a spectrum of varying cell biological and physiological responses based on the individual's genome and environmental exposure.

Could we have foreseen these events based on prior knowledge, and if so how should such predictions be utilized during drug development? The use of quantitative systems pharmacology (QSP) to guide drug development is becoming common [4, 5]. QSP approaches have been suggested for prediction of adverse events [6, 7]. Specifically for FAAH inhibitors, already in 2014, a QSP model that provides a mechanistic pharmacological understanding of drug action of FAAH inhibitors was published [8]. However, it appears that use of such modeling approaches to predict adverse events during drug development is lagging.

The increasing availability at reduced cost of high-throughput molecular profiling technologies for prediction of adverse events based on mechanism rather than phenotype models is rapidly receiving increased interest from regulatory authorities and pharmaceutical industry [7, 9]. Examples are academic research consortia such as the NIH-funded DToxS research center that develops cellular signatures for drug toxicity based on multiple human-derived cell lines, and similar European Union funded consortia such as EU-ToxRisk.

Investment by the pharmaceutical industry in pre-competitive public-private consortia could be a driver for a concerted effort to predict rare adverse events early during drug development in

order to bring safer drugs to patients. Access to robust systems models and integration with prior cell and tissue physiology knowledge as well as individual genomic information could provide a major pre-competitive boost to the pharmaceutical companies by reducing attrition [10]. A “virtual” Bell Lab that combines expertise in industry, academia and government regulatory agencies could play a defining role integrating different data streams and developing artificial intelligence based approaches to build a new generation of smart preclinical models to predict adverse events that can have robust clinical impact.

References

1. "Version anglaise : Minutes of the Temporary Specialist Scientific Committee (TSSC) meeting on "FAAH (Fatty Acid Amide Hydrolase) Inhibitors" of 15/02/2016 (08/03/2016)". Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM).
2. Kaur et al. What failed BIA 10-2474 Phase I clinical trial? Global speculations and recommendations for future Phase I trials. J Pharmacol Pharmacother. 2016 Jul-Sep;7(3):120-6
3. Johnson et al. Fulminant Myocarditis with Combination Immune Checkpoint Blockade. N Engl J Med. 2016 Nov 3;375(18):1749-1755.
4. Benson et al. Network-based discovery through mechanistic systems biology. Implications for applications – SMEs and drug discovery: where the action is. Drug Discovery Today: Technologies. 2015. 15 41-48
5. van Hasselt & van der Graaf. Towards integrative systems pharmacology models in oncology drug development. Drug Discovery Today: Technologies (2015) 15: 1-8
6. Berger & Iyengar. Role of systems pharmacology in understanding drug adverse events. Wiley Interdisciplinary Reviews: Systems Biology and Medicine 2011 3(2) 129-135
7. Bai & Abernethy. Systems pharmacology to predict drug toxicity: integration across levels of biological organization. Annual Review of Pharmacology and Toxicology 2013 Vol. 53: 451-473.
8. Benson et al. A Systems Pharmacology Perspective on the Clinical Development of Fatty Acid Amide Hydrolase Inhibitors for Pain. CPT Pharmacometrics Syst Pharmacol. 2014 Jan; 3(1): e91.
9. Verbist et al. Integrating High-Dimensional Transcriptomics and Image Analysis Tools into Early Safety Screening: Proof of Concept for a New Early Drug Development Strategy. Chem. Res. Toxicol., 2015, 28 (10), pp 1914–1925
10. Waring et al. An analysis of the attrition of drug candidates from four major pharmaceutical companies. Nature Reviews Drug Discovery 14, 475–486 (2015)

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