

Focusing on Target Safety

The development of new medicines is long, laborious, costly, and far too often results in failure, but the rise of artificial intelligence may be the solution to many, if not all, of these issues

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Despite the increase in drug approvals in recent years, drug discovery and development remain an uncertain and costly endeavour with depressingly high rates of failure (1). The era of Big Data and artificial intelligence (AI) offers the potential to manipulate huge amounts of data and discern patterns, offering scientists better insights and supporting better decisions than previously. Consequently, stakeholders across all disciplines are exploring ways to incorporate these powerful new approaches into their thinking. The identification of better drug targets, safer and more effective molecules, and improved patient selection should lead to better drugs as well as greater efficiency and decreased costs.

AI describes when a machine mimics cognitive functions such as learning and problem solving (see Box 1). There is much excitement in published literature and in the press around the many current and potential uses of AI in drug discovery and development. Recently, the ability of an AI platform to beat experts at poker caused more excitement in scientific literature and in the popular press (2-4). Overall, AI has great potential in enhancing success via learning and predicting patterns in biology, medicine, and chemistry. Regarding biology, AI could be used to explore unknown disease mechanisms, to analyse signalling pathways pointing to new potential drug targets, and has further utility in profiling those drug targets (5-6). Regarding chemistry, AI could be used to explore and define new chemical space, to suggest new drug structures, and for structure- and ligand-based virtual screening (7). Regarding medicine, AI has great use in analysing disease patterns in support of precision medicine, perhaps linked to individual genetics. There is additional interest in computational techniques to suggest new purposes for existing medicines based on a reverse relationship between the genetic profiles of the disease and cellular responses to drugs (7-9). AI is expected to make the hunt for new pharmaceuticals quicker, cheaper, and more effective (10).

Traditionally, drug discovery and development follow two broad paradigms; they could be driven by research aimed at

meeting an unmet medical need in a population or driven by basic (often academic) research that identifies new targets, pathways, and mechanisms that may have therapeutic use. Irrespective of the drivers, drug discovery has traditionally relied upon human intelligence to interpret data and predict outcomes. With its potential to digitise all aspects of this process, AI now brings almost limitless computational power to the detection of patterns, connections, and potential outcomes (see Image 1).

Examining the Failures

In the hunt for ways to make drug discovery and development more successful, there have been several excellent analyses of why drugs fail. Although the reasons for failure are usually complex and multifactorial, 'safety/toxicity' is cited as the predominant cause of failure (11-12). This realisation has led to a big focus within the pharma industry on 'derisking' projects early in discovery and development using a systematic approach to address key risks. A 5Rs framework (right target, right tissue, right safety, right patient, and right commercial potential) has been proposed and implemented by AstraZeneca (11). In a more academic or biotechnological setting, the TCP approach (right target, right chemistry, right patient population) is useful to focus teams on the optimal line of sight to drug registration (13). Toxicology is an integral part of this approach and must be taken into account at all stages and in all aspects of a drug project (see Figure 1, page 69).

Within the group of failed drug projects, research from Big Pharma companies has shown that around 40% of these failures across nonclinical and clinical development are attributable to safety issues associated with the therapeutic target itself (see Figure 2, page 69) (11). This is not surprising since many targets that are attractive in treating diseases are also likely to have important roles in normal biology, and their inhibition or activation could lead to unintended consequences. For example, in the case of TeGenero TG1412,

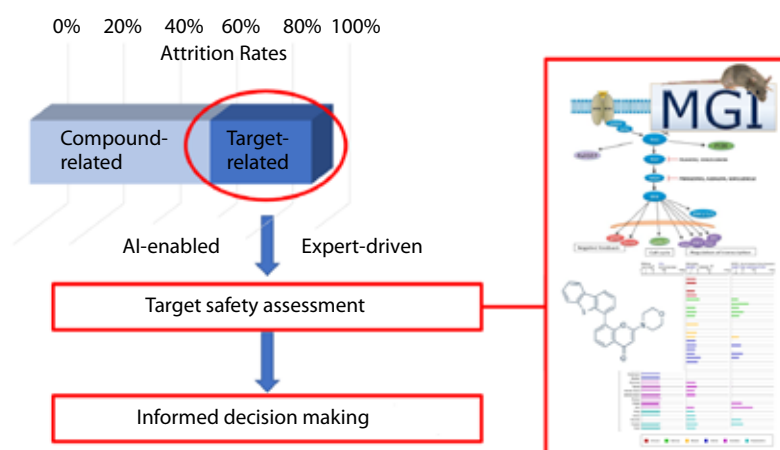


Figure 1: AI-assisted target safety assessments: issues related to the drug target account for >40% of preclinical and clinical failures. AI can be used to assemble a comprehensive, unbiased dataset comprising genetic, pathway, mutation, expression, paralog, and tool compound data. An AI-assisted, expert-enabled target safety review can support informed decision making leading to better project choices

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an absence of a thorough understanding of target biology led to a severe underestimation of clinical risk (14). So, wouldn't it make sense to maximise our understanding of the biology of a potential drug target in order to predict and manage issues before they arise?

Understanding the Targets

As a starting point to gaining an understanding of a drug target, there are bioinformatics platforms offered by Big Data companies that can collate and curate publicly available information from a variety of sources such as PubMed and MGI (15-17). More recently, companies have been exploring

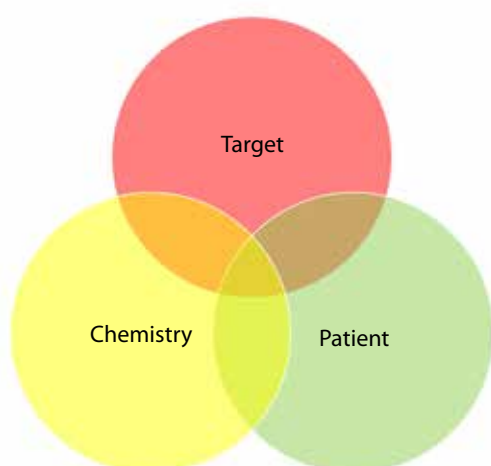
how AI can assist in collating this information; platforms such as Galactic AI use an advanced natural language processing platform that assesses and analyses scientific texts, providing a comprehensive set of the most relevant data in an unbiased way (6). Data collated includes information on signalling pathways, messenger RNA and protein expression patterns, the consequences of human mutations, genetic manipulation studies in transgenic mice, cross-species homology, paralogs, and tool/competitor compounds (see Figure 2). Using a combination of AI experts and the toxicology domain expert, specific applications (apps) that are target safety assessment (TSA) focused, can be built on the platform. For example, such an app could categorise, sort, and prioritise information

using tabs that filter for key data categories such as nonclinical species, target organ systems or clinical/nonclinical. Additionally, the dynamic feed provided by AI can flag new public domain findings relating to the target as they emerge.

Irrespective of whether the data are sourced via traditional bioinformatics platforms or via new approaches such as AI, the real value of a target safety assessment TSA comes with the quality of data interpretation. This requires an expert drug discovery toxicologist who understands the project team needs and can apply expert judgement on which risks are given priority in support of informed decision making. Unlike automated read-outs, an ideal TSA would summarise the current state



Image 1: Drug discovery and development has followed two broad paradigms; research aimed at meeting an unmet medical need in a population (LHS) or academic research that identifies new targets, pathways and mechanisms (RHS). With its potential to digitise all aspects of this process, AI now brings almost limitless computational power to both approaches via detection of patterns, connections, and potential outcomes



Toxicology – part of drug design

Figure 2: Toxicology is a key aspect of drug design and should be integral to thinking on drug targets, chemistry strategy, and patient population

of knowledge concisely, present potential safety risks, and offer a carefully considered and practical risk mitigation plan. Depending on the stage of the project, the AI tool can flag new findings to be assessed by the toxicologist, who would use expert judgement to evaluate significance and decide whether the overall risk-benefit profile is altered sufficiently to alert the project.

Planning for Success

As summarised by Richard Brennan, “An in-depth evaluation of target safety is an invaluable resource throughout drug discovery and development”. Key to this is the goal of characterising on-target toxicities to assist in early programme decisions and to “anticipate, monitor, and manage potential clinical adverse events” (18). A timely and focused TSA enhances the chances of running a successful drug project

“There are clearly limitations to what AI can achieve, and there is some way to go before we understand how these technologies can best be deployed to complement the years of experience of dedicated scientists”

Machine Learning

AI is when a machine is trained to think and act like a human. Machine learning is a field of AI that uses statistical techniques to give computer systems the ability to ‘learn’ from data, without being explicitly programmed. Deep learning goes beyond machine learning and uses algorithms inspired by the structure and function of the brain (so called artificial neural networks) to reveal hidden relationships between experimental observations and causal biological endpoints. Learning can be supervised (where each example is a pair of an input and desired output) or unsupervised (where the AI system is presented with uncategorised data).

and can maximise the return on limited resources. In this, there is no such thing as bad news; rather, TSAs support timely and informed decision making (19). AI is poised to play a role in enabling TSAs but a dataset, however extensive, is just the starting point to a TSA and is meaningless without the toxicology expert, who can ensure risks are prioritised in support of informed decision making (see Figure 3).

There are clearly limitations to what AI can achieve, and there is some way to go before we understand how these technologies can best be deployed to complement the years of experience of dedicated scientists. Currently, AI-enabled TSAs offer future proofing against the ongoing explosion of available data. However, the toxicologist remains pivotal

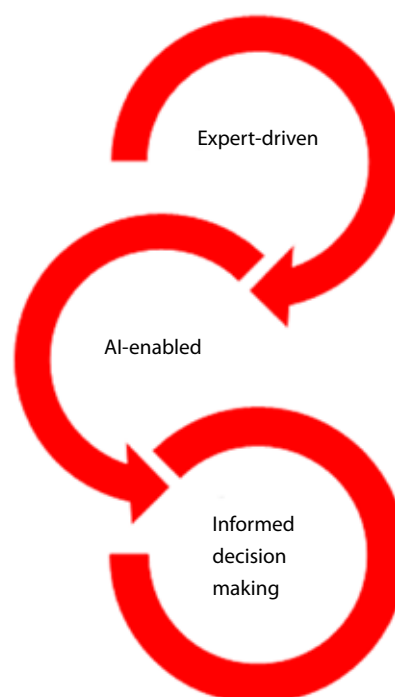


Figure 3: AI can assist expert toxicologists in informed decision making

“ AI cannot replace the expert who interprets the data, but experts who use AI may ultimately replace those that do not ”

in interpreting these data in the context of the project. Therefore, AI is able to suggest answers but cannot act upon them; implementation requires a domain expert with in-depth experience and judgement (20). We are a long way from the AI programme being able to actually propose key safety risks for each drug target, and, attractive as this is as a concept, it would require a step change towards structured programmes that have been ‘taught’ how to assess and interpret the data. Other limitations are around the quality of data input. It has been suggested that either not enough data or the wrong sort of data could be the downfall of AI, and companies are urged to invest in ‘better’ data, where better means more diverse and from high-quality sources rather than more of the same (20).

Overall, AI offers great potential in drug discovery and development. From early-stage drug discovery to clinical decision support systems, there are examples of how AI can improve efficiency and decrease costs. However, we must be careful to ensure AI does not over-promise. Regarding safety/toxicity, the use of AI to access a comprehensive, unbiased dataset provides an excellent starting point for the expert toxicologist to interpret the data, indicate key risks, and propose a risk-mitigation plan that can grow and evolve as the project progresses. Ultimately, AI cannot replace the expert who interprets the data, but experts who use AI may ultimately replace those that do not (adapted from Bedarek, 2019).

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