Computer simulations predict the cause of a drug's fatal neurotoxicity in a failed clinical trial

A new drug called BIA 10-2474, in development for pain management, caused severe side effects in a clinical trial in France in 2016. In the safety phase of the clinical trial, one healthy participant died from unexpected bleeding in his brain, while five others had less severe but clinically significant bleeding events. As this side effect was unanticipated even after years of pre-clinical research on this newly developed drug, which includes studies in cells and several types of animals (e.g. mice, rats, dogs, primates), the underlying cause or 'mechanism-of-action' of this neurotoxicity is unknown. Accordingly, novel and proprietary computer simulations, developed by Cyclica Inc. called Ligand Express™, were used to screen this 'small-molecule' drug against all known proteins, and found that BIA 10-2474 interacted with the protein it was designed to inhibit (fatty acid amide hydrolase) as well as approximately 300 additional human proteins.

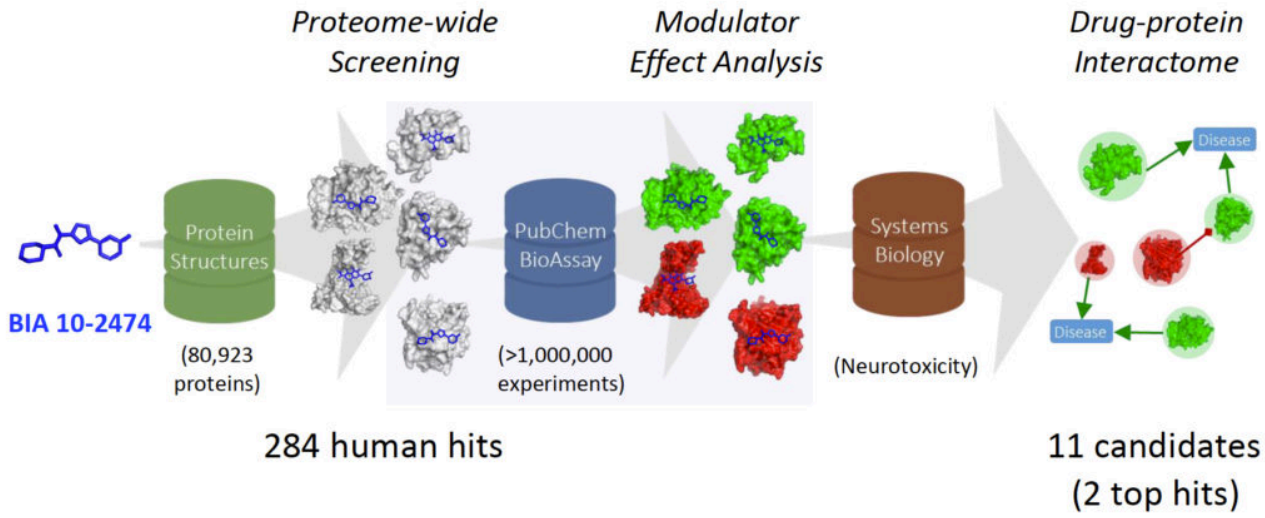

Fig. 1. Computer simulations predict the cause of fatal neurotoxicity for BIA 10-2474.
Screening the BIA 10-2474 drug against known proteins using computer simulations determined which human proteins are most likely to interact with this drug, how the function of these proteins will be affected, as well as which of these proteins are associated with the fatal side effects (i.e. bleeding in the brain). From this analysis, 11 candidate proteins were identified, two of which are blood coagulation factors (factor VII and thrombin) that were predicted to be inhibited by the BIA 10-2474 drug, and therefore are strongly associated with observed side effects of bleeding in the brain.

Importantly, when this list of proteins was further refined for keywords related to the clinical effects (i.e. brain bleeding, inflammation, etc.), it was determined that 11 candidate proteins were highly

enriched among this list. Further computational analysis of these proteins determined that the two highest ranking hits were essential blood-clotting factors (FVII and thrombin), and additional computer simulations predicted BIA 10-2474 would inhibit these two proteins, subsequently leading to anticoagulation or bleeding effects.

This study provides the first rational hypothesis and actionable insight into the mechanism of neurotoxicity for this investigational drug being developed for pain management. Furthermore, this computational approach could also facilitate off-target profiling for other drugs currently in development as potential therapies for other diseases.

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