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Commentary: Unexpected Novel Chemical Weapon Agents Designed by Innocuous Drug-Development AI (Artificial Intelligence) Algorithm

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Abstract

Recent publications reveal the disturbing information that a minor edit to an algorithm being used for designing legitimate drug candidates redirected the program in a way that resulted in the surprising design of novel chemical warfare agent candidates. Although this outcome was not the result of nefarious intent, and appropriate chemical defense authorities were notified, the potential implications of some misapplication of a drug-design algorithm for nefarious purposes are clear. This Commentary summarizes how otherwise benign Artificial Intelligence (AI) algorithms used for drug discovery can be easily reversed to design novel chemical warfare agents for which no effective antidote will be available, or perhaps even envisioned.

Keywords

Artificial Intelligence, Drug Discovery, Chemical Weapons, Machine Learning, Generative Model, Toxicity Prediction

1. Introduction

The application of artificial intelligence (AI) to the drug-discovery endeavor has seen a rapid progression in recent years due in part because of the promise of more efficiency and deeper data analysis, but most importantly, because of the

potential for revealing exciting unexpected results for therapeutic clinical candidates. [1]-[9] The number of publications on the topic has increased dramatically over recent years [**Figure 1**] and at least 40 models had been developed already by 2019. [10] The result is an acceleration of the DMTA (design-make-test-analyze) process by more rapid iteration. [11] [12] [13]

2. AI-Assisted Generative Model Drug Discovery

The "generative" model [**Figure 2**] is designed so that during a series of feedback iterations, positive attributes of efficacy and druggability are "rewarded" and negative attributes—particularly toxicity—are "penalized", thereby optimizing the outcome (potential drug candidates). Chemical structure candidates can be obtained from a variety of sources, including chemical libraries, medicinal chemistry insight, natural products, *de novo* computer design (*in silico*), or other. [8] [11] [14] In the normal process, simplistically, the candidate compounds (real or virtual) are: 1) screened and scored (rated) for efficacy for the therapeutic target; 2) screened and scored for desirable pharmaceutical features related to ADME (absorption, distribution, metabolism, and elimination), and potential drug-drug interaction (DDI); and 3) screened and scored for potential adverse toxicologic effects. Candidate structures with low predicted separation between efficacy and toxicity (low therapeutic index, TI) are not likely drug candidates, but *via* iterative artificial intelligence algorithms, lead to progressively better and safer possibilities (*viz.*, higher efficacy and lower toxicity).

3. Inverted Intent/Process

In the reported twist, the process was essentially inverted—toxicity, instead of therapeutic efficacy, was rewarded. [15] And a predicted low LD50 (potent lethality) was the goal and criterion for iterative optimization (**Figure 3**). The

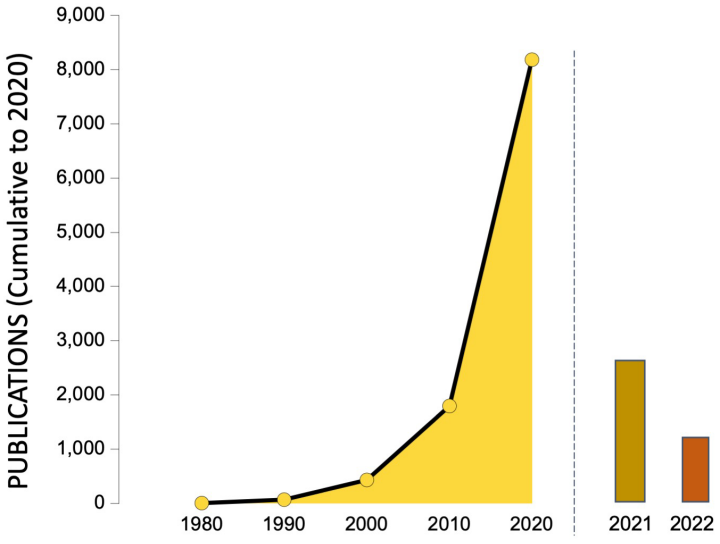

Figure 1. Search of PubMed using: ["artificial intelligence" or "machine learning" or "deep learning" or "neural network"] and [drug(s)].

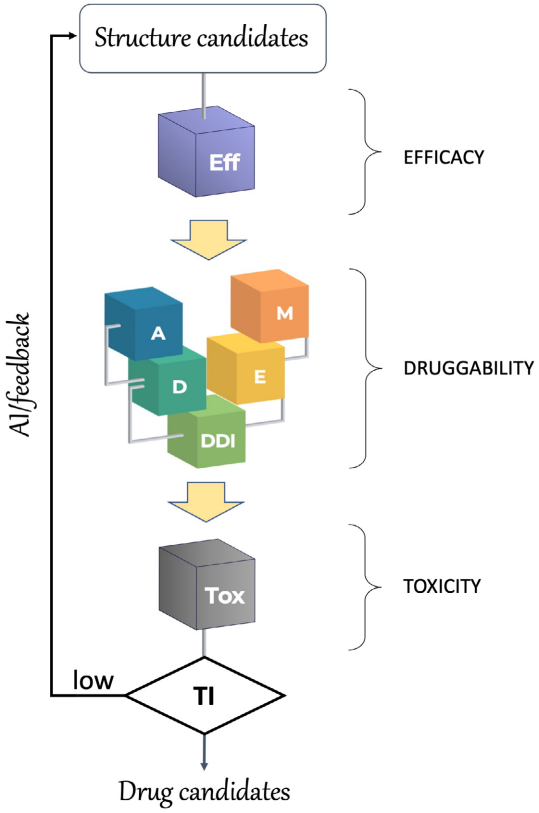

Figure 2. Chemical structures are tested virtually for therapeutic efficacy (Eff), druggability (ADME and drug-drug interactions, DDI) and toxicity. For drug-discovery, structures with low predicted safety (low therapeutic index, TI) are eliminated by AI-driven iterative process.

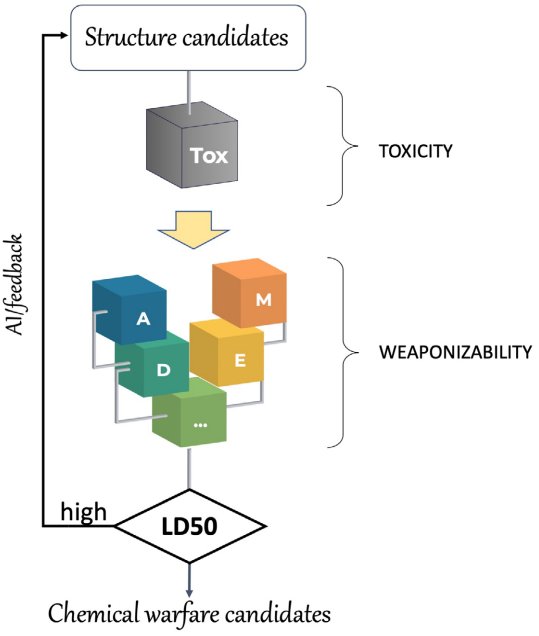

Figure 3. The drug-discovery flow was "inverted", and optimized for toxicity (LD50). The result was a surprisingly quick transition to discovery of highly potent potential chemical warfare agents.

investigators were surprised that in less than 6 hours the algorithm generated more than 40,000 chemical weapon candidates, some known (but not used in the training set), but many previously unknown. More than a thousand were predicted to be more potent than the notorious VX (venomous agent X). The seemingly innocuous generative machine learning model was designed to predict toxicity, but not as the desired endpoint. Rather the prediction of toxicity (as well as ADME parameters) was used as an aid to design compounds that have an attractive safety margin (therapeutic index), *i.e.*, separation of predicted therapeutic efficacy from predicted toxicity. Thus, the measure of toxicity was used as a negative screen rather than the desired goal, and the algorithm was designed to "reward" chemical structures of predicted therapeutic efficacy and to "penalize" chemical structures predicted to have serious toxicity. The inverting of the process resulted in an unquieting twist.

4. Conclusion

The reported example involved Collaborations Pharmaceuticals' code for designing molecules intended for potential development for treatment of Alzheimer disease. Chemical warfare agents were not on their radar screen. But prompted, the researchers found that a simple edit to their algorithm pivoted it away from designing life-saving molecules to designing life-taking ones. And there was a paradigm shift in the revelation. By this minor edit, gone was the assumed reassurance that chemical weapons conceived and designed by human thought processes could always be counteracted by human thought processes.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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