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Editorial

Exploiting Advances in Automation and Artificial Intelligence to Find Drugs for Neglected Tropical Diseases

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The last few decades have seen very impressive technological developments in the drug discovery and development field, and significant advances in treatments for for major diseases such as cancer and cardiovascular diseases, largely in the developed world. However, the so-called 'neglected tropical diseases' (NTDs), a large family of parasitic, bacterial, viral, and fungal diseases that are responsible for huge morbidity and mortality in the developing world, have not seen the same level of advances. The WHO identifies 20 major NTDs but do not include malaria and tuberculosis. NTDs affect nearly 2 billion people, including 0.5 billion children, and cause ~200,000 deaths per year[1]. While tuberculosis (TB) and malaria kill 1.6 M and 600,000 respectively. Its Global Report on Neglected Tropical Diseases 2023 (https://www.who.int/publications/i/item/9789240067295) states that, despite some progress in treatment and eradication of the most common debilitating NTDs, they still account for 14.5 million disability-adjusted life years. For the purposes of this Editorial, malaria and TB will be counted as NTDs.

Parasitic (e.g., malaria, African trypanosomiasis, leishmaniasis), bacterial (e.g., tuberculosis, leprosy), and viral diseases (e.g., rabies, Dengue fever, Chikungunya, Ebola) still kill 2.5 M people annually, and create misery and suffering for countless hundreds of millions worldwide. Sadly, infectious diseases affecting >1 Bn people in developing countries attract little donor funding, because those diseases are rare in wealthy, largely non-tropical countries. The cost of bringing a new drug to market is approximately US$2 Bn and pharmaceutical companies need to recoup this large, high-risk investment through the cost of the drug. Although the market is very large for NTDs, the ability of individuals or governments to pay for drugs is a major barrier to their development and sale. Philanthropic organizations such as the Bill and Melinda Gates Foundation, Stop TB Partnership, and the Medicines for Malaria Venture aim to bridge this gap.

The recent global coronavirus pandemic has shown how the traditional expensive and lengthy drug development pipeline can be dramatically reduced in a crisis. Rapid screening programs, fast structural biology programs on drug targets, use of computational design methods and machine learning (ML), and repurposing of existing drugs and natural products have resulted in new or repurposed therapies reaching patients in record time. The lessons learnt can and should be applied to finding treatments of NTDs where none currently exist, or better treatments where the current drug regimens are inadequate.

Computational drug discovery and repurposing methods can now provide very useful guidance for discovery new drugs or repurposing of existing drugs. Given the massive increase in use of robotics and automation for drug discovery, and the consequential increase in data, machine learning methods in particular offer great promise for cost-effective and rapid discovery of advanced therapeutics for NTDs in the short to medium term. The application of contemporary artificial intelligence (AI) and ML methods to discovery of drugs for neglected tropical diseases has been reviewed very recently.[2,3]

Machine learning has made stunning advances in predicting the 3D structures of protein targets for drugs, as exemplified by AlphaFold and its alternatives.[4] It is now possible to generate structures that rival those from experimental structural biology for most proteins. This provides an unprecedented way of rationally designing new drugs, or of repurposing existing drugs in record time and at low cost. An example of this was provided recently by Lam *et al.*,[5] who generated structures for multiple monkeypox proteins using AlphaFold2 for an in silico drug repurposing study. The expanded use of high throughput in vitro assays for NTD targets will also generate large quantities of data for training ML-based models of structure-activity relationships. Lack of chemically diverse training data for ML models is currently one of the major roadblocks to applying these powerful ML methods to the search for drugs to treat NTDs. Once adequate training datasets are available, it will be possible to use the full suite of advanced shallow and deep learning methods to generate models that can be used to understand mechanism of action, predict new drugs for trials, screen large databases

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of candidate molecules for leads (the recently-released ZINC-22 database of make-on-demand molecules contains >30 Bn compounds), and to automatically generate new active molecules using encoder-decoder and generative adversial networks.[6] There also the first examples of fully autonomous drug discovery systems that take an initial set of lead molecules and 'evolve' them towards a set of defined desirable properties (fitness functions) using AI methods such as evolutionary algorithms[7,8]. The spectacular increase in capability of general large language models like ChatGPT also has profound possibilities for drug design and discovery in general, and for NTDs particularly, as was described in a very recent Nature letter.[9]

Clearly, repurposing of existing drugs reduces the time and expense of clinical trials that are required for new chemical entities.[10] As existing drugs have already been through human clinical trials, their pharmacokinetics, efficacy, and toxicity profiles are well understood. Off-label use to treat NTDs is much simpler, cheaper, and faster than registering a new chemical entity, especially if the drug is off patent and generic versions are available. The value of this approach was shown during the recent SARS-CoV-2 pandemic and has been mooted as a useful strategy for NTDs[2]. Computational approaches to drug repurposing, including ML, have significant potential for rapidly identifying potentially useful drugs, clinical trials candidates, and approved natural products rapidly and cheaply.[11,12]

The massive increases in the availability data on NTD drug targets from ML-driven methods such as AlphaFold, the increased availability of NTD drug activity data from accelerated screens, and with the still unclear but exciting potential of large language generative models provides a paradigm shift for discovery of new and repurposed drugs for treating NTDs.

Author Contributions

David Alan Winkler: Conceptualization, Writing - Original Draft.

Conflict of Interest

The author reports no conflicts of interest.

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