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To Accelerate the Development of New Drugs, Dynamic Computational Models of Neuronal Circuitry are being used

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Abstract

With the failure rate of clinical trials for CNS illnesses reaching all-time low, new strategies are needed to reverse the trend. This paper looks back at the recent history of CNS drug development and proposes a new paradigm based on what has been learned. Following the initial wave of breakthrough therapies identified by detailed clinical observations, an emphasis on a phenotypic target-agnostic technique emerged, often resulting to beneficial pharmaceuticals with a diverse pharmacology. Because these highly selective molecules are unlikely to address the complex pathological phenotypes of most CNS disorders, the subsequent introduction of molecular biology and a focus on a target-driven strategy has largely dominated drug discovery efforts, but has not increased the probability of success. The use of preclinical animal models has lacked robust translational power in several circumstances. Quantitative Systems Pharmacology (QSP), a mechanism-based computer model of biological processes informed by preclinical information and strengthened by neuroimaging and clinical data, may be a new potent knowledge generation engine and paradigm for rational polypharmacy.

Keywords: QSP; Drug discovery; CNS

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Introduction

Drug development success rates in CNS illnesses are at an all-time low, with only a single digit chance of success in clinical trials. Many multinational pharmaceutical companies have abandoned neuroscience as a therapeutic area because of the high rate of late-stage failure. These developments are undoubtedly due to a number of factors, including our current lack of understanding of the pathophysiology underlying the majority of CNS disorders, which creates significant barriers to the development of appropriate preclinical models for effectively translating findings into clinical efficacy. Furthermore, many medications [1], particularly antibodies, fail to properly contact the molecular target or, as will be detailed, targets. CNS illnesses are unquestionably complicated, and the concept of a single target for these disorders has become increasingly illusory. From many years ago, molecular biology evolved into a mature field that produced a slew of strong tools, including deep sequencing, target cloning, and a variety of sophisticated transgenic rodent models. Advanced imaging techniques using PET tracers and other MRI sequences are also used. These advancements have resulted in a massive amount of data, which has necessitated the creation of strong algorithms. The philosophy behind these efforts was founded on the idea of "one gene, one protein, and one disease," which resulted in the discovery of single targets that were assumed to be linked to a specific disease. Following that, combining high-throughput capabilities and powerful SAR-driven medicinal chemistry, very effective and selective medicines were discovered. Unfortunately, there have been few new breakthrough medications found for CNS illnesses [2,3].

This is particularly sad because many people respond well to even the most widely prescribed antidepressants, and there are no effective medications for the treatment of neurological problems. In other indications, including as oncology and inflammation, rational target selection has had some success, but not in CNS illnesses. To stem the flow of clinical trial failures, it's worth revisiting the strategies used by earlier drug hunters to find effective medications and combining them with more recent advancements to generate fresh insights and tools for CNS drug discovery. Rather from being technology-driven, drug discovery programmes should be concept-driven (biology-chemistry). Starting with a very particular inquiry, it's critical to define the required methodologies and instruments – even if they're as simple as pharmacology or enzymology. If they

don't add to the answer, avoid the "nice-to-have" and attractive technology. Basic academic research has a distinct objective than drug discovery and development [4].

Furthermore, rather than a reductionistic approach, an integrated approach is required to handle the intricacies of the human brain. A drug development endeavour must be razor-sharp and laser-focused on identifying the optimum chemical for a certain disease indication. Short feedback cycle times, as well as early and on-going management buy-in, are critical for success. A variety of extremely selective medications have been created and tested in schizophrenia, mostly to target the cognitive impairment and negative symptoms associated with schizophrenia, based on evidence that various genes were engaged in distinct elements of schizophrenia. The discovery that CHRNA7, the alpha7 nAChR gene, was linked to the clinical phenomenology of schizophrenia, for example, prompted substantial clinical testing of a variety of alpha7 NAChR modulators. PDE10 inhibitors, Histamine H3 antagonists, mGluR2/R3 partial agonists, dopamine D3, dopamine D4, glycine modulators, 5-HT2A modulators, GABA modulators, AMPAkines [5], and neurokinin modulators are examples of other attempts to develop extremely selective medications. Most of these targeted drugs are now being developed in clinical trials due to a lack of efficacy.

Conclusion

The computer modeling's concentration on electrophysiological signatures in neuronal firing networks corresponds to a growing emphasis on cross-diagnostic symptom classes that are more closely and mechanistically tied to underlying neurobiological processes. Non-invasive technologies such as EEG and MRI imaging can be used to investigate the biological mechanisms behind these symptom groups. The computer model's ability to simulate these scenarios adds to the new paradigm's translatability.

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