Alkermes' Data-Driven Approach to New Target Ideation

By Craig Hopkinson, M.D., EVP, Research and Development, CMO, Alkermes

At Alkermes, we are committed to advancing new treatment options for people living with complex psychiatric and neurological disorders. As an organization with more than 30 years of neuroscience expertise, we understand the complex biological nature of central nervous system (CNS) disorders and the unmet needs facing patients with these conditions. With these patients in mind, my R&D colleagues work with great urgency, driven by our core value of Great Science, to identify and develop potential new medicines. This work begins with our New Target Team, a cross-functional team working to identify promising new molecules for the potential treatment of various CNS disorders.

Key Challenges in Drug Discovery and Development

It's no secret that the drug discovery and development process is lengthy, expensive and fraught with risk at every stage. For programs entering phase 1 across the industry, there is a less than 10% chance of final approval. Furthermore, approximately 50% of drugs fail in late-stage clinical trials due to low efficacy, meaning they do not show clinically meaningful improvement in the targeted disease or symptoms.

Developing medicines for CNS disorders is particularly challenging. A cluster of symptoms often characterizes these disorders and may overlap with others, adding further complexity to the treatment and diagnosis process. For example, while preclinical models provide a crucial foundation for evaluating the safety, potential efficacy and mechanism of a given potential treatment, they are often only attuned to a single symptom associated with a disease (i.e., reduced energy in major depressive disorder). This can lead to poor clinical translatability.

For these reasons, it is critically important to select the right target with a robust, biologically defined causal link to a disease early in the drug development process.

Our Approach

Over the past few years, Alkermes has implemented a rigorous, data-driven approach to ideate and prioritize new targets for additional study. Our goal is to identify targets with strong mechanistic and translational rationale that have the potential to be commercially viable. Elements of this strategy include systematic interrogation of diverse, human-centric data, input from a broad cross-functional team, and a focus on the neurocircuitry of both diseases and their associated symptoms to help establish a chain of translatability.

Our approach is supported by cutting-edge technology, including AI and machine learning models, which aid in efficiently refining our discovery process and help improve our chances of success.

Leveraging this approach, we design symptom-targeted experimental plans that utilize a focused selection of genetic, neuromolecular, cellular, electrophysiological and behavioral assays that are finely tuned to adjudicate the potential effect across the cluster of symptoms and target profiles.

Craig Hopkinson

A Look at Our Research

One recent example that benefited from our unique approach is the advancement of our orexin portfolio. Orexin neurons project from the hypothalamus into multiple brain regions and modulate downstream neurotransmitters. These neurons activate neurocircuitry that applies to multiple symptomatic domains, including wakefulness, mood, cognition, fatigue and attention.

> **Our target selection strategy is clear – we interrogate human data using AI to create a strong biological rationale, design and execute symptom-customized experimental plans, and hold ourselves to a high standard by fiercely triaging candidates**

Our lead orexin 2 receptor agonist, ALKS 2680, is currently being evaluated in three phase 2 studies for narcolepsy type 1, narcolepsy type 2 and idiopathic hypersomnia. Project Saturn, our orexin portfolio expansion strategy, is focused on research into harnessing the effects of orexin in the treatment of diseases beyond hypersomnolence disorders.

Through Project Saturn, we are leveraging our understanding of this neurocircuitry to pursue a multi-faceted preclinical research program based on quantitative, objective data. The three pillars include quantitative electroencephalography (qEEG) to assess brain wave activity, microdialysis to measure neurotransmitter profiles, and select behavioral assays to measure symptomatic activity in animal models. This robust assessment is designed to help us identify the most promising lines of development and evaluate the effects of orexin 2 receptor agonists either as monotherapy or combined with other mechanisms to extend the spectrum of pharmacologic activity.

As part of Project Saturn, we aim to advance our research of two orexin 2 receptor agonists, ALKS 4510 and ALKS 7290, which were identified in our preclinical program.

Moving Forward

Overall, our target selection strategy is clear – we interrogate human data using AI to create a strong biological rationale, design and execute symptom-customized experimental plans, and hold ourselves to a high standard by fiercely triaging candidates.

We know the drug discovery process is challenging, but we are committed to closing the gap in preclinical to clinical translation as we seek to build on our neuroscience expertise in pursuit of new medicines for patients.