Cyclica
www.cyclicarx.com

Informing drug discovery with AI and computational biophysics

Cyclica's drug discovery platform accelerates preclinical drug development by predicting the polypharmacological profile and medicinal properties of drug candidates.

Developing effective and quick-to-market medicines is a global priority. Off-target drug effects can be a major problem for getting urgently needed drugs to market. Drug target specificity and selectivity are important for avoiding effects on unintended targets, which can cause toxicity and are a major source of attrition during both preclinical and clinical development.

Cyclica, a global biotech company with headquarters in Toronto, Canada, that has been operational since 2014, takes a polypharmacology approach to drug discovery by considering first and foremost all potential target interactions of a drug molecule. Cyclica's integrated, artificial intelligence (AI)-augmented drug discovery platform enables multi-objective evaluation and design of drug candidates with favorable polypharmacological profiles and medicinal properties. By aiding the design of safer, more efficacious drugs, Cyclica reduces attrition rates and timelines to the clinic.

"We are unique in that we are taking a more holistic, yet personalized approach, to drug discovery by not looking only at one protein target or one well-characterized protein, but looking at the entire proteome and evaluating the polypharmacology of a given molecule," said Cyclica's co-founder and CEO Naheed Kurji.

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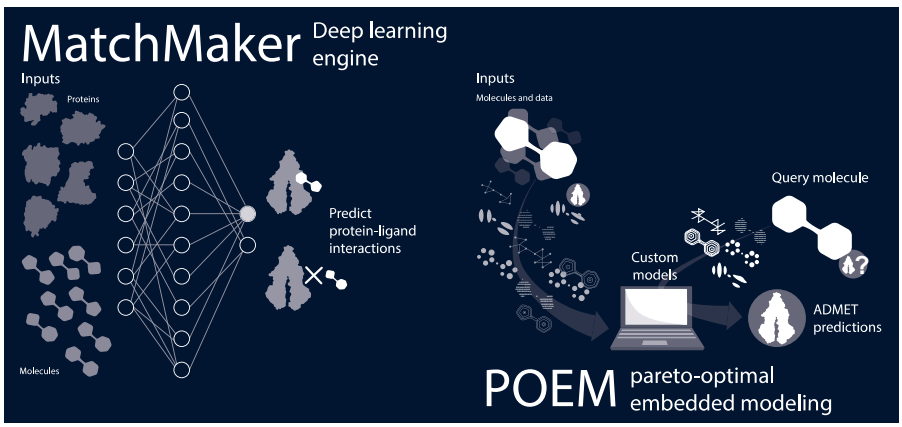
>
> Andreas Windemuth, CSO, Cyclica

Approaches for computer-aided drug design typically focus either on structure-based biophysics, which physically simulate how a molecule interacts with a specific protein at a given binding site, or on knowledge-based approaches that predict a molecule's activity from aggregated biological and chemical data. However, both approaches work best on molecule classes and protein targets for which a wealth of data exists; their ability to extrapolate findings to novel targets and chemistries is limited.

By leveraging both AI and computational biophysics, Cyclica's platform facilitates the design of molecules that target less well characterized proteins, while also shedding light on the molecules' mechanisms of action. Applications of Cyclica's platform span target deconvolution to drug repurposing and de novo design. The platform is powered by two machine learning engines, MatchMaker and POEM.



MatchMaker, a deep learning engine for proteome-wide ligand protein interactions, and POEM, a pareto-optimal embedded model for ADMET property prediction. ADMET, absorption, distribution, metabolism and excretion toxicity.

Matchmaker and POEM

Matchmaker combines molecular biophysics and deep learning to predict binding of potential drug molecules across the human proteome with high speed and accuracy. "In our validation studies we demonstrated that Matchmaker is faster and has better predictive power than molecular docking approaches for binding prediction," said CSO Andreas Windemuth.

Pareto-optimal embedded modeling (POEM) is a parameter-free supervised learning approach that predicts the medicinal properties of a molecule, offering insights into absorption, distribution, metabolism and excretion toxicity (ADMET) pharmacological properties and how they can be optimized. "When compared with other publicly available models for ADMET property prediction, POEM has come out consistently ahead," Windemuth said. "At Cyclica we consider the downstream medicinal and developmental properties of a molecule in the ligand design process, unlike other companies that think of them as an afterthought," he added.

Over the past 18 months, Cyclica has designed molecules for a wide range of diseases—including cancer, neurodegenerative and infectious diseases—that are progressing through preclinical development. "We have de novo designed molecules that have been synthesized, shown multitargeted biophysical activity, and can reduce tumor size in xenograft models," said Windemuth. "Showing prospective validation like this is critically important; we can't just say our cutting-edge approaches will work, we have to show it."

Strategic partnering model

To further catalyze productivity in early stage R&D with its platform, Cyclica is keen to create companies and build its internal portfolio through partnerships. "Our partnership model is focused on spinning out companies with academic institutions, taking equity positions in early stage biotech companies, forming joint ventures or, in some cases, sharing the asset ownership of the molecule," Kurji explained.

The company's goal to kick off 20 drug discovery programs across many therapeutic areas in 2020 has been far surpassed. By the end of the year Cyclica will have rights to close 100 programs. In addition, Cyclica has just embarked on its largest joint venture with the University of Toronto to develop ligands against 'undruggable' cancer targets and is expanding its efforts in non-human species. "At Cyclica, we believe that to drive sustainable progress in reducing attrition rates and timelines to the clinic, an avant-garde approach to drug discovery, both scientifically and commercially,

CONTACT
Jennifer Sacco, Director, Marketing & Communications
Email: jennifer.sacco@cyclicarx.com

Vern de Biasi, VP, Global Head of Strategic Partnerships
Email: vern.debiasi@cyclicarx.com