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Using AI to embrace patient heterogeneity

Auransa's AI-driven prediction of drug candidates and corresponding patient responders increases the chances of clinical trial success.

Everyone knows drug discovery takes time and money. Typically, drug targets are identified after years of collective research. Hundreds of thousands of compounds are screened against a small number of targets, and the most promising candidates are developed for clinical trials. However, many fail here, as they do not provide meaningful clinical benefit, partly because they are not tested in the appropriate patient population most likely to respond.

Auransa, an artificial intelligence (AI)-driven pharmaceutical company based in Palo Alto, California, has created a drug-discovery engine that bypasses the need for a drug target as a starting point. By analyzing diverse molecular data obtained from public data sources, the SMarTR engine can predict drug candidates for particular patient populations.

"We start by looking for recurrent biological signals across patient data sets," explained Viwat Visuthikraisee, a physicist turned entrepreneur, COO and co-founder of Auransa. "Repeated clusters or patterns of gene expression allow us to define patient subtypes".

After segmenting patient populations according to their disease biology, the engine starts crunching other patient data that could influence drug response (clinical, genetic, demographic). This allows an in-depth characterization of patient subtypes.

"The next step is to search drug-induced gene expression data in preclinical models to identify those that are good matches for the signature of disease subtypes," Visuthikraisee said. This effectively allows target- and disease- agnostic drug discovery.

Unlike conventional drug approaches, SMarTR is incredibly fast (Fig. 1), creating a strong pipeline for the company in a short period. "The whole process takes only about 24 hours of computational time," said Pek Lum, Auransa's CEO and co-founder. In this short period, the engine can detect patient subpopulations, identify biomarkers and preclinical models, and run an in silico computational analysis of close to 30,000 unique perturbations with more than half a million gene expression profiles. "It is a data science and engineering feat."

The engine searches through all types of compounds, including approved, investigational and natural ones. The predicted compounds are then ranked for further development taking into consideration their drug-like properties and novelty. In some cases, they are used as a starting point to create analogues and completely new drugs, whereas in others, the engine is identifying new therapeutic uses for agents that are already in the clinic.

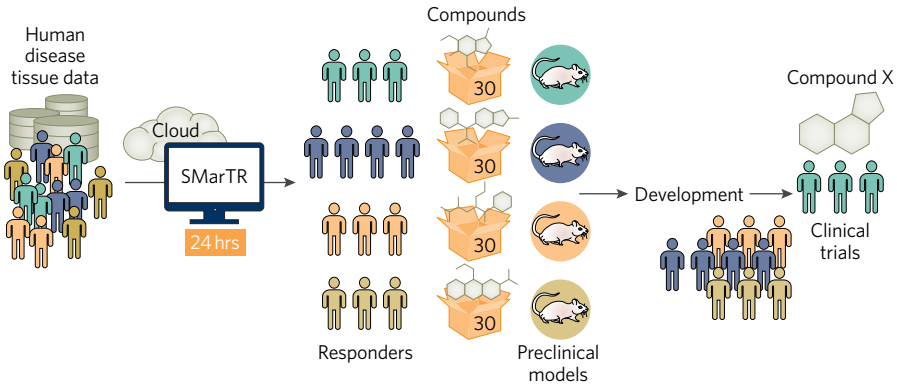

Fig. 1 | Auransa's approach starts from disease tissue molecular data and ends with therapeutics for responder patients. The target-agnostic, drug-discovery engine analyzes data from disease tissue to accurately predict drug candidates for particular patient subtypes. Typically, fewer than 30 predicted compounds have to be tested in preclinical models to find ones with development potential.

Putting the engine to the test

Auransa's preclinical team typically tests between 10–30 of the predicted compounds in in vitro or in vivo experiments. "Because we don't have to test thousands of compounds, we can carry out deep functional assays that would be too expensive, time consuming or simply not possible to do with hundreds or thousands of compounds," Lum added.

About half of SMarTR's predicted compounds show development potential after initial testing, and many are in different phases of drug development. The engine's unprecedented predictive power is being harnessed to build an internal pipeline of novel drug candidates for a broad range of diseases. "Because we don't go in with any assumptions, we have the opportunity to find something totally new," Visuthikraisee said.

Examples in preclinical development include AU-018, a cardioprotective agent that mitigates the cardiotoxicity associated with the chemotherapeutic agent doxorubicin whilst also increasing its anti-cancer activity; and AU-409, a compound that Auransa is developing for liver cancer. AU-409 has already finished GLP toxicology studies and is being prepared for clinical trials.

AU-409 is an RNA transcription modulator that specifically affects the expression of genes that cancer cells rely on for growth. "This is not another tyrosine kinase inhibitor, it is potentially a first-in class drug with a superior preclinical safety profile," Visuthikraisee explained.

Auransa's approach can be used to find lead compounds for diseases with no validated targets or disease biology, such as end-stage hormonal resistant prostate cancer. There are very few treatment options for patients who become resistant to hormonal therapy. Using SMarTR, Auransa has identified a number of potential compounds that could help them. One of them is extremely potent in killing cancer cells that are resistant to existing androgen receptor blockers. "We are now working on making a more drug-like compound and bringing it into the clinic, where we know which patients are likely to respond," said Lum.

In addition to finding and developing new drugs, Auransa's engine can also search for approved agents that could be repurposed. A recent project involved finding treatments for COVID-19. "Three out of 5 drugs identified by SMarTR are showing really good signs when tested alongside remdesivir in high-containment facilities," Lum said. This work highlights how Auransa's engine can speed up drug repositioning. Once the efficacy of a repurposed drug is demonstrated in the proposed use, in emergency situations, like a pandemic, it could go straight into clinical trials without the need to show preclinical animal safety again.

"We don't just want to get drugs into the clinic faster, we also want to target responders," Lum emphasized. By using huge diverse data sets that mimic patient heterogeneity in the clinic, SMarTR matches compounds to specific patient phenotypes from the get-go. This will translate into improved success in clinical trials.

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