KaiPharm Co., Ltd.
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Mining the transcriptome: using big data and AI to drive drug discovery the smart way

KaiPharm's KMAP platform combines drug-induced transcriptome profiles and artificial intelligence to accelerate drug development and drug repositioning.

The development of new drugs is time consuming, expensive and risky. Often, what appear to be promising drugs fail in the clinic, after much time and money has already been invested. A common reason for these failures is limited information about a new drug's mechanism of action (MoA). To reduce the risks of drug development, KaiPharm, based in Seoul, South Korea, has developed KMAP, which combines artificial intelligence (AI) with transcriptome profiling to generate deep insights into MoA and fuel efficient drug development.

In 2019, KaiPharm entered into a joint research agreement with Institut Pasteur Korea to use next-generation sequencing to populate the KMAP database with transcriptome profiles induced by thousands of drugs approved in the United States, the European Union, and Japan.

KaiPharm applies AI algorithms that compare the transcriptome profile of a drug candidate of unknown or ambiguous MoA with the thousands of profiles in the unique KMAP dataset to identify pattern matches that imply shared MoA. KMAP analysis is further integrated with experimental data on drug reactivity and drug-target interactions using bioinformatic, chemoinformatic and AI-driven deep-learning to deliver rich insights into drug MoA, including both on-target(s) and off-target(s) effects. The same approach can also be applied to identifying novel indications for failed drugs and natural products by comparing with the transcriptomic signatures of various disease models or patients (Fig. 1).

Another powerful application of KMAP is to identify novel MoAs and targets for previously approved drugs, which may point to new indications and markets for drug repositioning. It's well established that existing drugs can be successfully repositioned to treat indications beyond those they were originally developed for, but historically much drug repositioning has been driven by chance observations and serendipity. KMAP takes the luck out of drug repositioning.

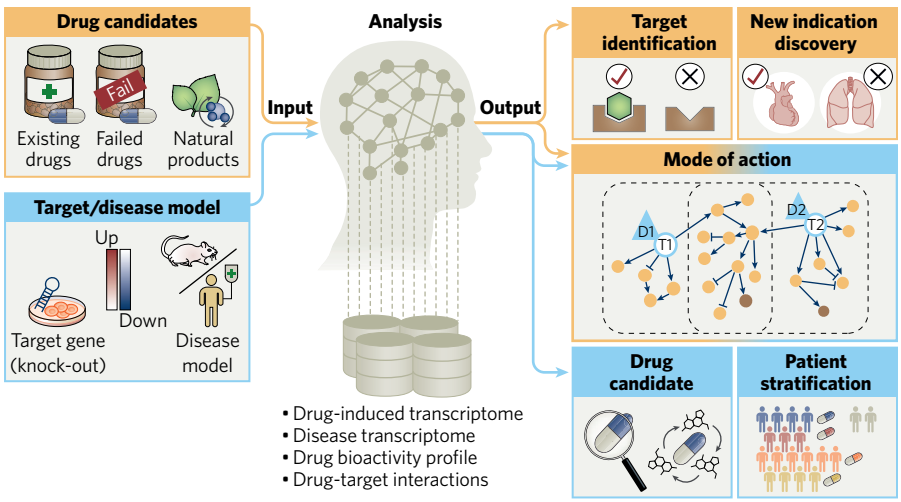

Fig. 1 | Accelerating drug discovery and drug repositioning. KaiPharm provides a comprehensive drug discovery platform for (i) drug-to-disease, and (ii) target/disease-to-drug projects.

Disease to drug capabilities

Beyond these drug-to-disease applications, KMAP also enables the reverse process, from disease to drug. KaiPharm scientists have published numerous studies showing how this can be done, particularly in the context of targets that have poor druggability, such as novel anticancer targets, as well as targets underlying chemoresistance. In one study, KaiPharm used transcriptomic profiles of lung cancers to identify an anti-metastatic drug starting from the poorly druggable target GALNT14, a putative driver of lung cancer metastasis. A comparison of the transcriptome profile of GALNT14 knockdown with those of known drugs identified bortezomib, approved for the treatment of multiple myeloma and mantle cell lymphoma, as inducing a similar transcriptomic response. In vitro and in vivo studies confirmed the previously unknown antimetastatic effect of bortezomib, which, like GALNT14 knockdown, attenuated transforming growth factor-β (TGFβ) and suppressed TGFβ-dependent metastatic gene expression.

In another study, a similar approach was used to tackle the challenge of chemoresistance. An analysis of the transcriptomes of chemoresistant cancer cell lines implicated the epithelial–mesenchymal transition as a common mechanism underlying resistance to chemotherapeutic drugs, and indicated ITGB3 as a promising target to overcome chemoresistance. The value of ITGB3 was confirmed in knockdown studies showing that eliminating ITGB3 sensitized cancer cells to conventional chemotherapeutics. Again, ITGB3 is a poorly druggable target, so a search was initiated to find drugs that mimic the transcriptome-level changes caused by ITGB3 knockdown, which identified atorvastatin, a competitive inhibitor of HMG-CoA reductase used to treat cardiovascular diseases, as a novel candidate for repositioning as an antichemoresistance drug. This application is being extended to diverse disease areas such as musculoskeletal and metabolic diseases.

Further applications of KMAP

Another important application of KMAP is for pharmacogenomics and patient stratification. As an illustration of how KMAP can be used, KaiPharm scientists employed transcriptome analysis of cancer cell lines to gain a better understanding of resistance to erastin, a synthetic lethal compound against cancers expressing oncogenic RAS that inhibits cystine/glutamate antiporters and induces a form of programmed cell death called ferroptosis. This analysis revealed that the activity of transcription factors, including NRF2 and AhR, serve as important markers of erastin resistance, knowledge that can be used to guide erastin therapy to those patients likely respond to therapy.

KaiPharm offers KMAP's transcriptome analysis and big-data mining technology platform for collaboration or as a service to pharmaceutical companies to achieve their goals of saving time, cutting costs, and improving success rate. An AI pharma is paving an alternative route to the development of new drugs, and breathing new life into old ones.

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