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Institute for Theoretical Medicine Inc.

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A one-stop shop for de novo drug discovery

Deep Quartet, a drug discovery platform developed by INTAGE Healthcare and the Institute for Theoretical Medicine (ITM) uses AI technologies to design new lead compound structures based on pharmacophore models.

Since 1992 INTAGE Healthcare and its affiliated companies have been delivering high-quality marketing research, real-world data analysis and a range of contract research organization (CRO) services. In April 2019, INTAGE Healthcare established an in silico drug discovery support department with the acquisition and integration of Kyoto Constella Technologies, a Kyoto University venture company.

The Institute for Theoretical Medicine Inc. (ITM) is a company specialized in chemoinformatics and the design for protein-protein interaction inhibitors. ITM has 17 years' experience in developing in silico drug design tools using chemoinformatics and machine learning technologies.

INTAGE Healthcare and ITM have collaborated to develop and launch Deep Quartet, a drug discovery platform that helps pharmaceutical companies design new drug structures using artificial intelligence (AI) technologies, such as machine learning (Fig. 1).

"The idea for Deep Quartet came from a desire to make AI useful to medicinal chemists in a practical workflow," said Ryuta Murakami, director at INTAGE Healthcare. "We are building a system that not only performs calculations to design new molecular structures, but also facilitates compound synthesis through our collaboration with partner companies," Atsushi Yoshimori, ITM president added.

Deep Quartet's service offering doesn't just propose new chemical structures to its clients, it synthesizes them too. "We offer a one-stop service, whereby pharmaceutical companies give us a set of requirements and we can deliver new compounds within a few months," Murakami added. This is proving an attractive proposition for many pharmaceutical and drug discovery venture companies.

3D drug design with AI

Pharmacophore models that describe the essential features for a molecule to interact with a specific target receptor in space, are widely used to discover, develop and analyze new therapeutic agents. Medicinal chemists can easily convert a protein-small molecule interaction to a pharmacophore model. However, it is much harder to generate drug-like molecular structures from pharmacophore models.

This is where deep generative modelling can help. Deep generative modelling is a deep learning framework for automatically discovering and learning the regularities or patterns in the input data so that the model (in this case a pharmacophore) can be used to generate new examples that plausibly could have been drawn from the original data. Deep Quartet uses deep generative modelling to convert pharmacophore models to molecular structures.

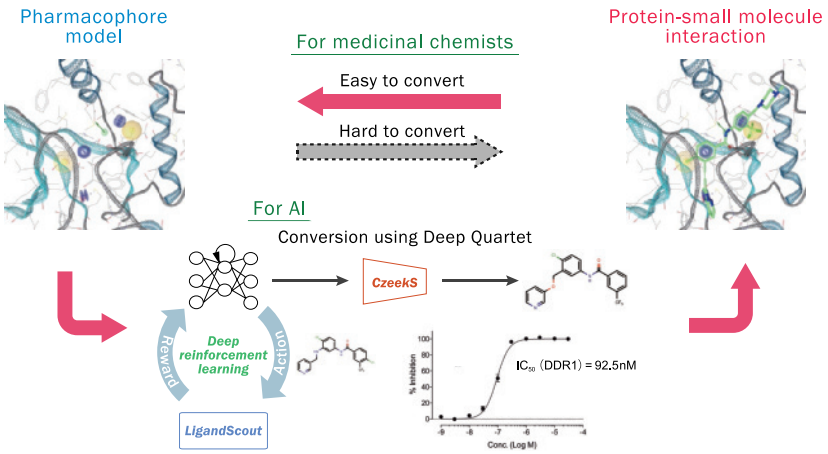

Fig. 1 | Rationale for Deep Quartet platform.

"We found that by using compound 3D information in deep learning we can find new compounds with strong inhibitory activity, highlighting the importance of 3D-structure in designing efficient lead compounds," Yoshimori explained.

Deep Quartet's workflow has four components: deep reinforcement learning to generate chemical structures from pharmacophores; LigandScout, a software tool to derive 3D pharmacophores from structural data of macromolecule/ligand complexes in a fully automated way; CzeekS to predict the selectivity of the generated compound structures with regard to target proteins such as kinases based on assay data; and the indispensable input from medicinal chemists.

"The knowledge of medicinal chemists is very important in deciding which structures will be selected for synthesis and how they will be synthesized to optimize the chances of clinical success, from both efficacy and safety standpoints," said Murakami.

INTAGE Healthcare and ITM have many ongoing collaborations designing new inhibitors against target proteins, in some cases against binding pockets that have not been targeted before. They are also actively conducting their own research and have published work using Deep Quartet to design new inhibitors against the angiopoietin-1 receptor TIE2 and discoidin domain receptor 1 (DDR1) that could be used to suppress cancer growth[1,2].

In both cases, pharmacophore models were generated from the crystal structure of the receptor in complex with known inhibitors. In the case of DDR1, from the over 4,000 structures with high-affinity binding scores generated by Deep Quartet, nine were selected for synthesis. One of the compounds exhibited a potent inhibitory activity against DDR1 (IC_{50} value of 92.5 nM).

INTAGE Healthcare and ITM are striving to develop more practical AI technology and help companies discover new drugs faster. Murakami and Yoshimori will continue the endeavour to develop an interface that bridges the gap between cutting-edge AI technology and medicinal chemists.

1. Yoshimori, A. et al. *Chem. Pharm. Bull.* **68**, 227–233 (2020).
2. Yoshimori, A. et al. *ChemMedChem* **16**, 955–958 (2021).

CONTACT
Ryuta Murakami, Director
INTAGE Healthcare Inc.
Tokyo, Japan
Email: murakami-r@intage.com