Oral Presentation 5

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口頭発表５
『創薬応用（その他）』
Drug Discovery application

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Taro Kakuzaki
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"Search for preventive drugs against Cisplatin-induced nephrotoxicity using public database and electronic medical records."
Eri Wakai
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"Search for preventive drugs for drug-induced neuropathy using medical information database"
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O2-05

Deep generative model for designing antibody from antibody library data

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Keywords: Antibody, Display library, Machine Learning, AI Drug Discovery

Antibodies are currently indispensable tools for therapeutic and biological research. Recently, NGS is frequently used to screen a lot of clones to acquire antibody with strong affinity from an antibody library panning using phage display technique. However, the frequently read antibody sequences do not necessarily have the desirable property due to restriction of sequence diversities of antibody libraries. Therefore, it is difficult to find the antibody sequences with strong affinity only based on sequenced data.

To address this problem, we employ long shot term memory network (LSTM) which is one of the popular deep generative model to design sequences with the desirable property. We employ a trained LSTM model to generative virtual sequences and then prioritize generated sequences according to likelihood based on it. We applied our method to in-house antibody library data and confirmed that our generated sequences have higher affinity than frequently read sequences. Moreover, we showed that likelihood of trained LSTM model correlates well with binding affinity. From our results, our LSTM based sequence generation and prioritization procedure is quite useful for acquiring strong binder and expanding library space from antibody library data.

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O2-06

Search for preventive drugs against Cisplatin-induced nephrotoxicity using public database and electronic medical records.

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Keywords: Cisplatin, Nephrotoxicity, Palonosetron, Public database, Real world data

Cisplatin (CDDP) is used widely for the treatment of several types of cancer. CDDP-induced nephrotoxicity is serious adverse events, previous treatment such as hydration therapy is insufficient to prevent nephrotoxicity [1]. In the present study, we investigated novel preventive drugs against CDDP-induced nephrotoxicity using public databases and electronic medical records. Using public databases related to gene expression profiling (Gene Expression Omnibus [2] and Connectivity map [3]), we identified palonosetron, a 5HT3-receptor antagonist, as the candidacy of effective preventive drugs for CDDP-induced nephrotoxicity. Using the Food and Drug Administration Adverse Event Reporting System (FAERS) database, we revealed that the reporting odds ratio of palonosetron for CDDP-induced nephrotoxicity was 0.56 (95% CI: 0.199 – 0.929) whereas no significant signals were not found with other 5HT3-receptor antagonists. Moreover, we retrospectively investigated the effects of palonosetron and other 5HT3-receptor antagonist palonosetron in 135 patients who received CDDP and fluorouracil therapy at Mie University Hospital. The rate of nephrotoxicity in the palonosetron group (17%, n = 77) was significantly lower than that in the ramosetron group (33%, n = 58). Severe nephrotoxicity greater than Grade 2 (by the Common Terminology Criteria for Adverse Events version 5.0) was more observed in the ramosetron groups than the palonosetron groups. These findings suggest that palonosetron can reduce CDDP-induced nephrotoxicity. This study was approved by the Ethics Committee of Mie University Graduate School of Medicine and Faculty of Medicine.

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O2-07

Search for preventive drugs for drug-induced neuropathy using medical information database

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Keywords: drug repositioning, medical information database, adverse event

Drug repositioning enables identification of novel uses of approved drugs. It is cost effective and has a shorter development period than conventional drug discovery. In recent years, various databases including a medical information database have been utilized for drug development. In this study, we aimed to identify prophylactic drugs for oxaliplatin-induced peripheral neuropathy (OIPN) to facilitate drug repositioning, utilizing medical information databases.

First, we analyzed the Library of Integrated Network-based Cellular Signatures (LINCS) of the National Institutes of Health (NIH) and extracted 23 therapeutic drug candidates counteracting OIPN-related gene expression changes. We searched for approved drugs that reduce OIPN using the FDA Adverse Event Reporting System (FAERS). Analysis using a medical information database revealed that simvastatin, used to treat dyslipidemia, significantly reduced reports of OIPN. Its neuroprotective effect was evaluated by the von Frey test using OIPN model rats. Simvastatin significantly reduced oxaliplatin-induced hyperalgesia. In model rat nerve tissue, the mRNA expression of the antioxidant enzyme Gstm1 increased with statin administration.

We, therefore, conclude that drug repositioning, utilizing a clinical database, would allow drug discovery for various diseases.