Current status of drug development in academia

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Through the infrastructure development of Translational Research Sites with government supports, translational researches that lead basic research outcomes to clinical development have been activated. As a result, pharmaceuticals and medical devices development originating in academia have been vitalized. The drug discovery originating in academia has been active since pharmaceutical companies introduced the idea of open Innovation. As one of the Translational Research Sites, the Clinical Research, Innovation and Education Center, Tohoku University Hospital (CRIETO) has been coordinating about 10 investigator-initiated clinical trials every year and providing support for over 200 development seeds. Based on the current situation, I will present the future prospects of drug discovery originating in academia from the standpoint of supporting the seeds development.
Kyoto University has a background of abundant basic research with beautiful science, and research for clinical application is also thriving to return these results to society.
iACT, an academic research organization in Kyoto University Hospital, connects with on- and off-campus researchers, finds potential candidates for clinical application, provides support for appropriate funding and clinical trials.
In recent years, some researchers completed pre-clinical evaluations such as pharmacological tests, toxicity tests, and pharmacokinetic tests of low molecular weight compounds discovered by academia, and manufactured investigational drugs by contract for clinical application. There are also many research proposals related to iPSCs-derived regenerative medicine or repurposing of approved drugs based on screening using iPSCs.
iACT aims to accumulate a wide range of knowledge and experience, and to apply them for better and faster development by supporting research proposals without limiting the disease area or the products categories.
LAT1 (L-type amino acid transporter 1: SLC7A5) is an amino acid transporter. While normal cells intake amino acids by LAT2, tumor cells intake amino acids by LAT1. In pancreatic cancer, LAT1 is overexpressed in tumor cells, and high expression of LAT1 is a predictive factor of poor prognosis. To date, LAT1 competitive-inhibitors, such as BCH and JPH203, were developed, and they are reported to be effective against various cancer cells in vitro and xenograft model. However, LAT1 non-competitive-inhibitors have not been developed.

Recently, we developed a LAT1 non-competitive-inhibitor and confirmed its anti-cancer effect against several cancer cells in vitro and xenograft model. Its oral administration also improved overall survival of genetically engineered mice with pancreatic ductal adenocarcinoma. After examining several nonclinical tests for the safety, we decided to move to the next step to acquire clinical proof of concept. To this end, we planned an investigator-initiated first in human clinical trial. After approved by institutional review board and clinical trial notification to PMDA, the trial has started and is ongoing. In the present session, we introduced our experienced process and various challenges to the investigator-initiated clinical trial.
Investigator-Initiated Clinical Trial of HGF Plasmid Product

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It has been known that hepatocyte growth factor (HGF) is produced along with hepatic and renal disorders and promote regeneration of injured organs through the proliferative effects on (1) vascular endothelial cells, (2) myocardial cells, and (3) lymphatic endothelial cells. The mechanism of action of the HGF plasmid product is as follows; HGF plasmid is introduced by injection into skeletal muscle/myocardium, HGF protein is released outside muscle cells via the transcriptional/translational process within muscle cells, the angiogenesis and lymphangiogenesis though the mechanism of (1), (2), and (3) result in an improvement of symptoms of chronic obstructive arteriosclerosis, heart failure, and lymphoedema with amelioration of blood and lymphatic fluid circulation.

For the angiogenesis in the lower limbs, the data from the investigator-initiated clinical research at Osaka University (P1/2), company-sponsored clinical trials (P3), and the investigator-initiated clinical research by Advanced Medical Care B (P3) were used for the new drug application. For the angiogenesis in the heart, the investigator-initiated trial (P1) of Osaka University was conducted. For the lymphangiogenesis, the investigator-initiated trial (P2) of Asahikawa Medical University as well as the company-sponsored trial (P1/2) are ongoing.

For development of products for treatment of rare diseases, as examples of industry-academia cooperation, we will introduce how we prepared for implementation of each investigator-initiated clinical research and investigator-initiated clinical trials, as well as what kinds of issues are there and how we have dealt with these issues to solve them.
Overview of Life Intelligence Consortium “LINC”

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In November 2016, we established the Life Intelligence Consortium (LINC), a collaboration organization between industry and academia and between life science and IT industries to advance AI development in the life science field. LINC consists of about 100 companies and organizations including IT companies and life science companies such as pharmaceuticals, medical care, and healthcare. With the support of academia from Kyoto University, RIKEN, etc., LINC aims to promote the health care field and related industries based on the AI strategy. In this lecture, I will introduce the details of research at LINC from the viewpoints of system pharmacology, ADMET, clinical data analysis, and natural language processing, and discuss the possibilities of AI and big data in the pharmaceutical industry.
Analysis of electronic medical record data, which is clinical real-world data, is expected to create new knowledge including new drug discovery targets. In LINC, projects such as stratification of diseases, detection of adverse events and discovery of unmet medical needs are in progress using electronic medical record data in collaboration with academia, life companies and IT companies. In this presentation, we will introduce an example of data analysis for renal disease using hospital-scale data conducted at Kyoto University Hospital, and discuss the possibility of using clinical real-world data for future drug discovery.
"Drug repositioning" has been attracting attention as a drug discovery strategy to overcome the recent slowdown in new drug development. Drug repositioning is a technique for discovering new effects of known drugs and redeveloping them as new indications for other diseases. Known drugs have already been confirmed for human safety and pharmacokinetics, and information such as compound production methods can be reused. Therefore, the drug repositioning approach is expected to reduce developed time, risk, and expenditure. Today, pharmaceutical companies are increasing to reuse their own drugs for the drug repositioning approach. In Life Intelligence Consortium (LINC), pharmaceutical companies, IT companies, and academia are developing together in more than 30 projects. In this talk, we will introduce the developed AI technology in one of the projects, "drug repositioning". In this project, the AI models that predict the target protein, drug efficacy, phenotype, etc. from the compound structure is constructed. The developed AI models can be expected to contribute to the target prediction of active compounds with unknown mechanisms of action, search for new drug discovery targets, and the new indication prediction by reprofiling known drugs.
Towards a system combining ADMET prediction AI and de novo structure generation AI

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RIKEN

To efficiently drive drug discovery process, it is essential to improve the profile of ADMET, which is a collective term for endpoints related to pharmacokinetics and toxicity, as well as enhancing the activity and efficacy on a target protein. In this presentation, we will give an overview of the current status of ADMET prediction AI and de novo structure generation AI that are being promoted through AMED "drug discovery informatics project" and the activities of LINC (Life INtelligence Consortium), an AI drug discovery consortium on all Japan scale headed by Prof. Okuno in Kyoto University. Also, issues toward a new drug design AI system that combines above mentioned two types of AI models will be discussed.
JDream Expert Finder: A Search Engine to Find Young Promising Researchers

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The authors and G-Search Limited are collaborating to develop a search engine "JDream Expert Finder" (JDEF) as an outcome of the project-8 in the Life Intelligence Consortium (LINC). JDEF has a function to find young promising researchers, who, so far, have only a little publication in the literature database of Japan Science and Technology Agency (JST). Using conventional citation indicators such as h-Index, it is inadequate to measuring young researchers' performances. Therefore, we have focused on the betweenness centrality in co-authorship networks as an alternative indicator. As JDEF has utilized a growth model of Japan Society for the Promotion of Science (JSPS) research fellows, thus, it is able to search the other young promising researchers from the JST database.