Agilent Case Study: Japan Tobacco Inc. Central Pharmaceutical Research Institute

Exploring New Drug "Seeds" Using a High-Throughput Mass Spectrometry System

Japan Tobacco Inc. (JT) was established in 1985, and it took over the tobacco and salt businesses of the Japan Tobacco and Salt Public Corporation. In addition to the tobacco business, which accounts for approximately 90% of sales, JT has now expanded into the processed food business, focusing on frozen noodles, frozen rice, frozen baked bread, packed cooked rice, and seasonings, as well as the pharmaceutical business, focusing on prescription drugs. We interviewed Dr. Yoshiji Hantani of the Biological/Pharmacological Research Laboratories at the JT Central Pharmaceutical Research Institute about his uses of high-throughput screening (HTS) to discover new drug candidates.

Creating original and innovative drugs for patients suffering from diseases around the world

In 1987, JT expanded their business into the pharmaceutical field with the belief that through respecting science, technology, and people, they will contribute to patients' lives. JT continues to make concerted efforts in research and development with the desire to quickly deliver original and innovative drugs to patients suffering from diseases around the world. Since 1993, JT's Central Pharmaceutical Research Institute has driven their research and development. The Central Pharmaceutical Research Institute is a comprehensive facility consisting of multiple laboratories focused on chemical research, biological/pharmacological research, product development, drug metabolism and pharmacokinetics, and toxicology research. The institute specializes in small-molecule drugs, mainly in the three fields of a) the cardiovascular system, kidneys, and metabolism, b) immunology and inflammation, and c) neuroscience. The Biological/Pharmacological Research Laboratory is tasked with conducting evaluations of new substances. It is here that Dr. Hantani conducts HTS for compound discovery.

Dr. Yoshiji Hantani

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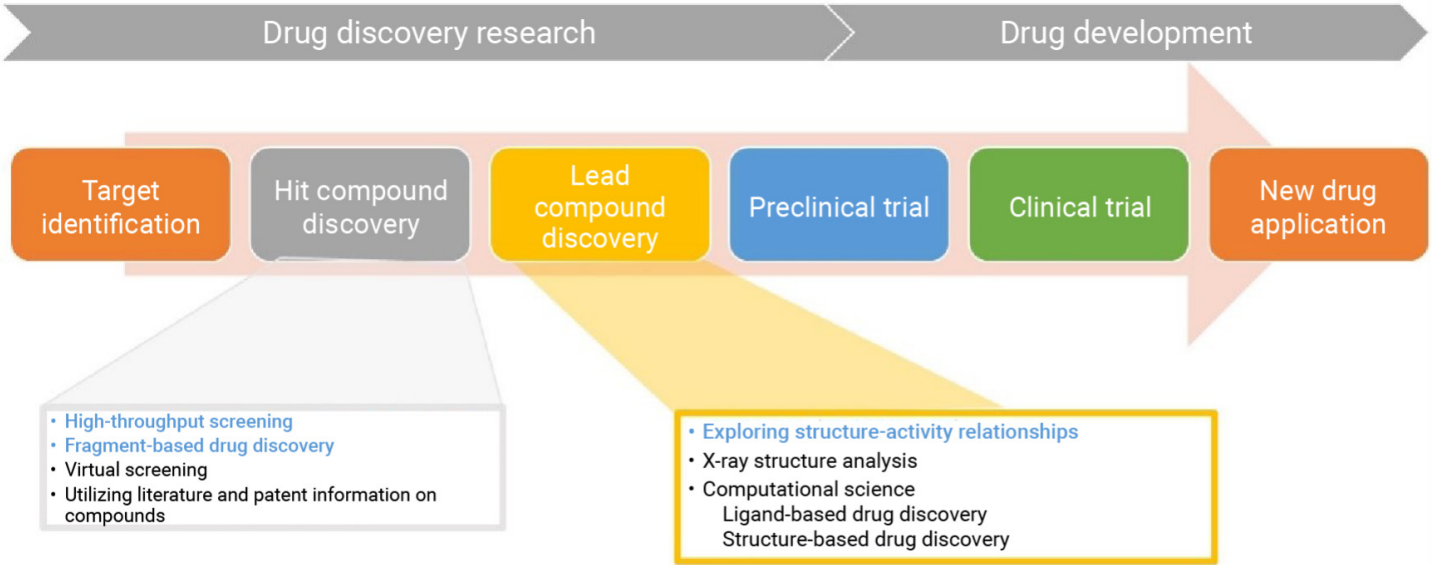


Drug discovery research process

The drug discovery research process: How to discover “seeds” for original, innovative drug

In general, new drug development starts with identifying a target; for example, selecting a protein related to a disease. In recent years, artificial intelligence (AI) has become an important tool in the identification of these targets. Once a target is identified, the next step is hit compound discovery, which involves finding a compound that has pharmacological activity on that target. Methods for discovering hit compounds include reviewing literature and patent information on compounds, computer simulations, and random screening to find compounds that have pharmacological activity. This search can span hundreds of thousands, or even millions, of compounds registered in a library. Next, lead compound discovery optimizes and refines hit compounds to a level that demonstrates efficacy in cells or animals depending on the research goal. The resulting lead compounds can be thought of as the "seeds" of new drugs. The structures of the lead compounds are further optimized to improve activity and safety before the compounds move on to preclinical and clinical trials.

Analytical instruments that support the discovery of new drug seeds

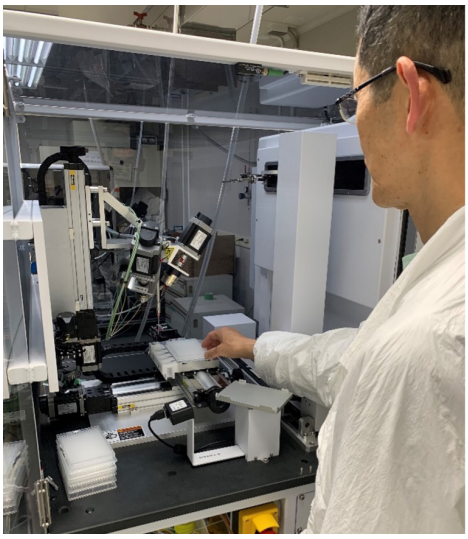
Hit compound discovery through random screening and lead compound discovery requires analyzing and screening many compounds. For this purpose, HTS is useful. Since 2000, JT has been working on HTS based on optical properties, using technologies like fluorescence analysis. In 2012, a decision was made to incorporate high-throughput mass spectrometry (HT-MS) to improve efficiency and drive further productivity. Dr. Hantani had experience in protein analysis using mass spectrometers, conducting research on lipids and exploring fragment-based drug discovery (FBDD).

While the speed of fluorescence analysis makes it a good choice for HTS, the unique capabilities of MS are often required for hit compound discovery, FBDD, and exploring structure-activity relationships (SARs) for lead compound discovery.

"One of the advantages of MS is that it can detect natural substrates and products without labeling," Dr. Hantani said. "For example, MS is suitable for lipid analysis. In other cases, where substrates are difficult to label, MS is also used. In the case of fragment screening, interferences can be a problem with methods based on optical properties due to the high concentration. We choose MS for this case as well."

MS screening may also be used to eliminate false positives and false negatives after screening based on optical properties.

Which high-throughput MS systems are used for hit and lead compound discovery?



Following the successful implementation of RapidFire 360, JT added RapidFire 400 to their lab.

The high-throughput MS system that JT chose in 2012 was the Agilent RapidFire 360. In addition to the advantages mentioned earlier, Dr. Hantani commented that this choice "was determined by a number of factors, including that we had read in the literature of another pharmaceutical company who had used RapidFire to screen 100,000 compounds." Dr. Hantani noted, "The throughput, which allows 384 samples to be processed in one hour, met our expectations. We often used it for fragment screening, and were able to complete screening of 30,000 compounds in about two weeks."

In 2021, JT decided to expand their instrumentation with the addition of an Agilent RapidFire 400 connected to an Agilent 6495C triple quadrupole LC/MS. "In particular, tests to detect changes in intracellular substrates are difficult to establish using evaluation systems other than those that use mass spectrometers. But, using the RapidFire 400, we were able to establish a stable evaluation system. This enabled us to efficiently evaluate the SARs of synthesized compounds and contribute to improving their activity," Dr. Hantani said.

The RapidFire 400 is now easier to use than ever before—it can accommodate 1536-well plates, it is equipped with a temperature-controlled sample storage unit, and it offers improved connectivity to the integrated plate handler robotics and mass spectrometers.

Why has RapidFire been used at JT Central Pharmaceutical Research Institute for over 10 years?

RapidFire offers label-free detection of natural substrates and products while eliminating the interferences observed with optical techniques. The service and support you can expect from Agilent were also a significant factor. "Agilent has accumulated data, so when you ask questions about, for example, selecting the right cartridge chemistry for your application or setting the conditions for your mass spectrometer, you can get an accurate answer. Also, when you call or email the customer support, you will get a response right away," Dr. Hantani said.

Future drug discovery: Using AI and the ingenuity of researchers

Considering recent trends in drug discovery, Dr. Hantani believes that exploring new modalities will be important. In the field of drug discovery, it is often said that "all the low-hanging fruit have already been picked"—in other words, there are no more targets that are easy to find, the only remaining targets are hard to find. To explore hard-to-find targets, new modalities such as targeted protein degradation (TPD), protein interaction stabilizers, and covalent compounds are being explored worldwide. In turn, mass spectrometers are extensively being used. Dr. Hantani, who has been observing the field of drug discovery for decades, said, "It is common for old technologies to be combined with new technologies. In drug discovery, it is important to value old technologies while keeping an eye out for adding something new to it."

Dr. Hantani believes that as AI is increasingly being used in HTS in drug discovery, mass spectrometers will become increasingly important. The data that AI uses as its base will become extremely important when using AI, and mass spectrometers make it possible to obtain large amounts of data. "Data obtained using mass spectrometers are robust and reliable. The combination of data obtained from mass spectrometers and AI will be used more and more," Dr. Hantani has predicted.

However, using AI does not necessarily make it easy to find drug candidates. Dr. Hantani said, "New modalities in drug discovery, such as targeted protein degradation, have been found, and I think the number of modalities will continue to increase. In such a situation, the ingenuity of researchers is required regarding how to approach finding drug 'seeds.' We will continue to exercise our ingenuity through friendly competition, and JT hope to develop and deliver original and innovative drugs as soon as possible, and make patients happy."

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