FIGHTING DEADLY DISEASES ON MULTIPLE FRONTS

From novel cancer-fighting microRNAs to new types of drug manufacturing facilities, Japan is breaking NEW GROUND IN CLINICAL RESEARCH.

The complexity of diseases, and the challenges inherent in developing new drugs to treat them demand a multipronged approach to research and development.

Two initiatives headed by Hidetoshi Tahara, a professor in cellular and molecular biology at Hiroshima University in Japan and the CEO and founder of spin-off company PURMX Therapeutics, Inc., exemplify this strategy of tackling diseases simultaneously on multiple fronts.

BENCH TO BEDSIDE

MicroRNAs are short snippets of RNA that control the expression of genes. They have been implicated in the development of cancer, but they are also emerging as promising therapeutics for various cancers. Now, researchers at Hiroshima University are focusing on the development of promising anti-cancer drugs using senescence-associated microRNAs. MicroRNA-based therapeutics are very rare, with only four currently being tested in clinical trials globally, and the senescence-associated microRNA therapy is the only programme of its kind in the world.

Early in 2021, Tahara started a clinical trial assessing the safety, tolerability and efficacy of a new RNA-based drug that targets malignant pleural mesothelioma. This deadly and treatment-resistant cancer affects the lining around lungs and has a poor prognosis, with most patients living less than one year after diagnosis. Worldwide, more than 25,000 people die every year from this rare cancer.

▲ Drug-development facilities that employ good manufacturing practices are needed globally.

gorodenkoff/iStock/Getty

This cancer is common in people who have had long exposure to asbestos. A common building material in the 1960s, asbestos is being removed and phased out now. However, it is still used in some countries, and the World Health Organization (WHO) estimates that about 125 million people around the world are still exposed to asbestos in their workplaces. Because Japan was one of the world's largest importers and users of asbestos, Tahara worries that the number of cases of this cancer will increase in the near future.

With no effective treatments available, Tahara decided to focus on an unconventional angle against this deadly cancer: ageing. One hallmark of cancer cells is their immortality. Unlike normal human cells, which go through the natural process of senescence, cancer cells live on, multiplying endlessly and invading different parts of the body. Tahara and his team designed a screening system for the microRNAs that targets the molecular pathways used by this cancer to remain immortal.

The microRNA developed by Tahara builds on previous findings showing the potential of several microRNAs to induce senescence — a state in which cells no longer divide — in cancer cells. It targets the molecular ageing switch of this cancer, effectively making cancer cells mortal while causing no damage to normal cells. This novel therapeutic concept may herald a new generation of cancer therapeutics targeting cancer senescence.

Data from preclinical studies in mice have shown promising results and this microRNA-based drug has also shown good outcomes when treating cancer stem cells.

Tahara is now taking his therapy to patients through two investigator-initiated and first-in-human clinical trials, currently being developed in Japan. Phase I and II clinical trials may start as early as 2024. Once this treatment reaches patients, it may be used in combination with chemotherapy or immunotherapy, Tahara says.

REVOLUTIONARY FACILITY

Beyond novel therapeutics, Tahara, who is vice president of Hiroshima University for academia–government–industry collaboration, is also paving the way for a new research facility that can revolutionize drug development in Japan. Good manufacturing practice (GMP) is an international set of principles and procedures that help ensure that therapeutic goods such as drugs and vaccines are of high quality. All drugs, vaccines and medicinal products need to go through a GMP process before they can reach patients. With this idea in mind, Hiroshima University is aiming to create Japan's first Peace & Science Innovation Ecosystem (PSI) GMP Education and Research Center. Set to open in 2026, this facility will support the development of vaccines and other therapeutic products. In addition, it will have a strong focus on education, providing GMP training to different stakeholders, from graduate students to researchers and educators.

The idea for creating the PSI GMP Education and Research Center originated during the COVID-19 pandemic, when Japan tried to make mRNA and other vaccines, but failed. "The government's thinking is that for the next pandemic, we should be able to make vaccines in Japan," explains Tahara. With this goal in mind, the Japanese government has committed about 3 billion Japanese yen (US$21 million) to fund the creation of the GMP centre.

The PSI GMP Education and Research Center is seeking to overcome the key hurdles Japanese scientists currently face when developing novel drugs.

"SUCH FACILITIES ARE ESSENTIAL FOR ACADEMIA TO DEVELOP INNOVATIVE THERAPEUTICS"

VALLEYS OF DEATH

These hurdles, which Tahara dubs 'valleys of death', hinder the translation of basic research into clinical applications.

They involve the best practices researchers need to follow during all stages of drug manufacturing, from the development of optimal chemistry, manufacturing and control (CMC) to GMPs for the design of pharmaceutical products. Also, a key hurdle is the effective design of a target product profile, from the early stages of drug development to the design of non-clinical/clinical studies aimed at commercialization. Another obstacle is research into CMC, Tahara explains.

The pharmaceutical industry is currently primarily responsible for drug discoveries, says Tahara, where more than 70% of these discoveries originate from academic start-ups. However, relying on pharmaceutical companies limits the potential of developing drugs, such as those targeting rare diseases. "If academia does not overcome valleys of death during development, the probability of innovative vaccines and drug discovery being put to practical use will decrease," says Tahara.

The PSI GMP Education and Research Center aims to overcome these hurdles, providing Japanese researchers the opportunity to develop the complete pipeline of drug development. "Such facilities are essential for academia to develop innovative therapeutics, but are in short supply both in Japan and abroad, and it will be very important to support them," says Tahara.

From the educational angle, this new centre will join forces with the University of Southern California to provide support in accordance with guidelines developed by the International Council for Harmonisation. GMP education is critical for overcoming the shortage in human resources in GMP manufacturing facilities.

Taken together, these two initiatives at Hiroshima University — using microRNA to make cancer cells mortal and the establishment of a GMP centre — are set to change the landscape of clinical research in Japan, heralding a new era of drug development. ■

▲ Drugs based on small segments of RNA called microRNA (pictured here) are showing promise for inducing senescence in cancer cells.

Artur Plawgo/Science Photo Library/Getty

HIROSHIMA UNIVERSITY

www.hiroshima-u.ac.jp/en

PURMX THERAPEUTICS

www.purmx.com/en

Advertiser retains sole responsibility for content