A central management goal for the Fujifilm group is to help resolve social issues through our business activities, and by developing products and services through our proprietary technologies.

We will use leading-edge, proprietary technologies to provide top quality products and services that contribute to the advancement of culture, science, technology and industry, as well as improved health and environmental protection in society. Our overarching aim is to help enhance the quality of life of people worldwide.

True to this corporate philosophy, Fujifilm has been creating value from innovation since our beginning as a photographic film company. The Fujifilm group now consists of about 300 consolidated subsidiaries worldwide, focused on three main business fields: healthcare & material solutions, imaging solutions, and document solutions. In this magazine the healthcare area will be explored.

All the businesses we have diversified into are grounded in photographic technologies, which have significant potential for a broad range of applications. Using our expertise in chemistry, biology, process engineering, nanotechnology, and artificial intelligence, we create innovative solutions that improve life for people across the world.

Fujifilm finds creative solutions to challenging problems by both looking to the future, and building on our traditional strengths. Together, we will “Never Stop” moving forward to create a sustainable society with a high quality of life for all.

Kenji Sukeno
President and
Chief Operating Officer

Shigetaka Komori
Chairman and
Chief Executive Officer
A picture is worth a thousand words, as the adage goes, but to the FUJIFILM Corporation, it is worth so much more. In 2000, photographic products accounted for 60% of Fujifilm sales and two-thirds of its profit. But with the market shifting away from film to digital cameras, Fujifilm’s core business was threatened. It had to try a radical reformation to survive and thrive.

Led by its CEO, Shigetaka Komori, the company took stock of its technological capabilities and decided to focus on six business areas: digital imaging, optical devices, highly functional materials, graphic systems, document solutions, and healthcare. It was Fujifilm’s vast expertise in photography, under innovative leadership, that enabled it to reposition itself as a leading company, while honouring its photographic assets.

Fujifilm had had a longstanding presence in the medical diagnostics domain, producing X-ray film in 1936, two years after the company was formed, and entering the endoscope market in 1971. The company created the world’s first digital X-ray diagnostic imaging system in 1981. Since then, the company has developed a variety of clinical digital technologies, and launched SYNAPSE, a medical picture archiving and communications system, in 1999.

Komori and the team realised that, in addition to its strengths in diagnostics, the company’s history of research excellence in film had yielded a wealth of knowledge in a range of fields — fine chemistry, optics, engineering, analysis, nanotechnology — that could also be applied to cosmetics and dietary supplement areas, and further treatment areas such as pharmaceuticals.

These in-house resources, combined with a series of strategic mergers and acquisitions including FUJIFILM Diosynth Biotechnologies, FUJIFILM Cellular Dynamics, FUJIFILM Irvine Scientific, FUJIFILM Toyama Chemical and FUJIFILM Wako Pure Chemical, to bolster Fujifilm’s cell biology and pharmaceutical capabilities, helped the company make a rapid and strong entry into the pharmaceutical and life science markets.

The healthcare fields of disease prevention, diagnosis and treatment now accounts for more than 20% of Fujifilm’s total sales, about US$5 billion. And more than a decade on from the company’s entry to the treatment field, cell biology products, such as induced pluripotent stem cells, biopharmaceuticals including gene therapy and cell culture media, are an integral part of the company’s portfolio.

The stories in this magazine explore the fields from which Fujifilm approaches healthcare such as, drug discovery using life science-based tools and artificial intelligence (see p13, 17, 27), drug development (p5, 14, 29), manufacturing of high-quality biopharmaceutical products (p7, 21, 24), and diagnosis with medical informatics and cutting-edge technologies (p11, 15, 19).

Through Fujifilm’s formidable portfolio, advanced technologies, and bold innovation, it continues to be a major contributor to medical discovery, and ultimately to help enhance the quality of life of people worldwide.
The exterior of the Fujifilm Advanced Research Laboratories in Kanagawa sports a special symbolic image — an owl, which represents the Roman goddess Minerva. In the preface to Hegel’s *Elements of the Philosophy of Right*, the philosopher famously writes, “The owl of Minerva begins its flight only with the onset of dusk.”

Minerva, in Roman mythology, was the goddess of crafts and war and the personification of wisdom. The owl was her sacred bird. When a civilization or an epoch came to an end, Minerva would release the owl and have the large-eyed bird appraise the age — what kind of era was it, how did it come to an end? Then, with this appraisal in hand, she would prepare for the age to come.

In Fujifilm’s case, the company’s near twilight came with the end of its peak years producing photosensitive materials, and the forward-looking Advanced Research Laboratories was to serve as a base camp for the creation of new core technologies. It was to serve the purpose of Minerva’s owl.
‘TRUE REGENERATIVE MEDICINE’: STEM CELL THERAPIES NEAR CLINICAL TESTING

A new facility allows Fujifilm scientists to manufacture induced pluripotent stem cells (iPSC) for human therapeutic products.

The opening of a multi-product cleanroom facility in early 2020 marks the beginning of a new chapter for FUJIFILM Cellular Dynamics Inc.

For more than a decade, this US subsidiary of Fujifilm has sold research-grade cells to the pharmaceutical industry for screening drugs and modelling diseases in the laboratory. Now, with the ability to create cells designed to meet the strict US regulatory standards for current Good Manufacturing Practice (cGMP), the company is stepping into the realm of regenerative medicine and preparing for clinical testing of its stem cell-derived product candidates.

Getting to this point has been a trial in itself. “Ever since we decided to start cell therapy programmes, we had to go back and look at every reagent we buy, every method we use, the scalability of our protocols and more, and then re-develop and re-optimize everything for human therapeutic use,” says Chad Koonce, director of cardiac cell therapy at FUJIFILM Cellular Dynamics headquarters in Madison, Wisconsin.

To have the $21 million facility up and running, with manufacturing planned for 2020 and beyond, is “all really exciting,” Koonce says.

The company currently manufactures more than a dozen cell types — including nerve cells, immune cells, and organ-specific cells of the liver, brain and heart — all of research-grade quality. At the new ultra-clean production site, the company will begin to generate four types of cells ready for clinical development with potential for expansion into other areas.

The initial four are dopamine-producing neural cells, cardiac progenitor cells, retinal cells, and immune cells. All are derived from human induced pluripotent stem cells (iPSCs) — skin or blood cells switched back to their pluripotent state. Using FUJIFILM Cellular Dynamic’s proprietary protocols, technicians then coax the iPSCs to form highly pure populations of the specialized cells of interest.

CLOSE AT HEART
Koonce was among the team that developed the process for making GMP-grade heart muscle cells and their precursors, known as cardiac progenitor cells. The specified version of these cells, called cardiomyocytes, are easier to fabricate, notes Koonce, but studies have shown that the cells, when implanted in the heart, sometimes beat out of sync with neighbouring tissues, leading to potentially fatal arrhythmias. Cardiac progenitor cells are expected not to spontaneously contract at the time of injection, reducing this initial safety concern.

“The key is that these cells are primed to become cardiomyocytes,” Koonce explains. “We can inject these cardiac progenitor cells directly into the damaged area of the heart and these cells will then differentiate. We’re actually allowing the cells to further develop once engrafted.” Koonce’s group is working with the team led by cardiologist,
Emerson Perin, at the Texas Heart Institute in Houston to evaluate the cardiac progenitor cells in a pig model of chronic artery blockage. So far, Perin’s team has injected the cells into approximately 10 pigs with experimentally induced heart failure.

Running a catheter through each pig’s groin, they deliver hundreds of millions of cardiac progenitor cells directly at the site of injury. Using an electromechanical mapping system, they build three-dimensional renderings of the heart chamber before and after treatment. They also perform complete post-mortem tissue work-ups on pig hearts. “The early sense we have is that this all looks very promising,” Perin says. “It’s true regenerative medicine.”

**COLLABORATIONS**

FUJIFILM Cellular Dynamics is spearheading development of the cell therapies for heart failure and Parkinson’s disease. For its eye disorders programme, the company, in 2016, spun off a venture, Opsis Therapeutics, which is developing two kinds of iPSC-derived retinal cells aiming to restore sight for people with age-related macular degeneration, which destroys central vision, and retinitis pigmentosa, an inherited condition marked by loss of peripheral and night vision followed by loss of central vision.

In 2018, the company also teamed up with Versant Ventures, a healthcare investment firm, to create Century Therapeutics, a biotech company that aims to develop immune cell therapies for cancer using FUJIFILM Cellular Dynamics’ iPSCs.

“We’re taking advantage of the almost limitless renewal capacity of the iPSCs and doing really unique engineering to get functionalities that you really can’t get with any other sort of platform,” says Michael Naso, vice president of cell engineering at Century, which is based in Philadelphia, Pennsylvania.

Existing immunotherapies of this kind require bespoke engineering of immune cells for each individual recipient. Many companies are trying to develop off-the-shelf alternatives that work for everybody. The problem is that the biological starting material needed for any ready-made cell product begins with blood drawn from a healthy human volunteer, and this process is fraught with batch-to-batch variability that can affect safety, efficacy, availability and cost.

By comparison, with iPSC-derived immune cells, “we just go back to that frozen vial of cells, so there is no variability,” Naso says. “It is the same every single time.”

And there may lie the greatest strength of FUJIFILM Cellular Dynamics’s stem cell engineering technologies. Many researchers and companies can transform iPSCs into immune cells, heart muscle, retinal tissues or neurons. “But making the cells over and over again at the same purity and at the same scale is hard,” Koonce says.

Fortunately, he adds, “it’s something FUJIFILM Cellular Dynamics has had a lot of practice doing.”

Stem cells can differentiate into a wide variety of cells, including heart muscle cells, neural cells and blood cells.
Three factors are critical for a successful, high-performing bio-production process, according to Tom Fletcher, scientific director at FUJIFILM Irvine Scientific.

Of paramount importance is the cell line. The cell culture media is the second factor, and third, the configuration of the bioreactor, including settings such as dissolved oxygen or agitation rate.

The focus of FUJIFILM Irvine Scientific’s Custom Media and Services Department is improving cell growth conditions by optimizing the cell culture media. “Without a good cell line, you are never going to have a good process, but the importance of the cell culture media cannot be underestimated,” Fletcher explains.

A cell culture medium provides the necessary nutrients and factors for cell growth, as well as regulating the pH and the osmotic pressure of the culture, so choosing the right one is critical to the success of products, such as biotherapeutics and biosimilars.

**CHOOSING INGREDIENTS**

The right media depends on the type of cells being cultured, the manufacturing process and the product being made. Typically, media for biotherapeutic production or cell therapies don’t contain serum (a component of blood plasma associated with a higher chance of variability and contamination) and have a high nutrient concentration to sustain high cell densities and enhance cellular productivity.

“Our aim is to match an optimal media composition to the particular nutritional requirements of a specific cell line and thereby double or triple the level of product,” says Fletcher. By optimizing the cell culture media, companies will be able to achieve performance.

**PROVIDING A GOOD FOUNDATION**

Optimizing cell culture media is key to achieving high yields of biotherapeutics and biosimilars.
goals before scaling up bio-production processes.

The team supports manufacturing process development for companies developing vaccines, monoclonal antibodies, recombinant proteins, gene therapies and cell therapies.

“For our customers, cell culture media are raw materials used in the manufacturing process,” says Fletcher. “They want to avoid any variation that might impact the growth and productivity of their cell cultures, and reduce manufacturing performance,” he adds.

Various cell lines have very different nutritional requirements, even if they are derived from the same parent cell. Although most cell culture media have similar components such as amino acids, salts, vitamins, trace metals, buffers and sugars, both the absolute and relative concentrations of nutrients can be modified to boost cell growth and sustain particular metabolic behaviours.

Finding the right mix of these components for a particular cell line not only increases the production of biotherapeutics, but improves their quality by supporting the desired post-translational modifications that aid glycosylation, protein folding or secretion, and prevent aggregation.

For example, the Custom Media team has recently developed a new culture media supplement for biotherapeutic development, called BalanCD Gal Supplement. The new formula increases galactosylation of glycoproteins during biotherapeutic manufacturing, to help achieve the right glycan profiles for improved product quality and antibody efficacy.

The increased production of biotherapeutics for the treatment for diseases, such as cancer, diabetes, rheumatoid arthritis and other non-communicable diseases, has created an unprecedented demand for cell culture media. FUJIFILM Irvine Scientific’s Custom Media is now servicing large scale biotherapeutic production processes for a variety of cell lines by supplying liquid media batches of up to 10,000 litres or up to 7,000 kg of powder culture media, equivalent to 280,000 litres when hydrated.
Anyone old enough will remember the media frenzy that followed the birth in 1978 of the world’s first baby conceived through in vitro fertilization. Since then, millions of babies have been born through assisted reproductive technology (ART).

ART procedures require high-quality, reliable media and technologies for the delicate processes of separating, incubating, transferring and freezing eggs, sperm, and embryos.

FUJIFILM Irvine Scientific has vast experience and expertise and is a pioneer in this field. Established in Irvine, California in 1970 as Irvine Scientific Sales Company (Irvine Scientific), the company has manufactured media for ART since 1986, only five years after the technology began in the USA. The company — which was acquired by Fujifilm in 2018 and renamed FUJIFILM Irvine Scientific — also has facilities in Japan and the Netherlands, and is a leader in the design and manufacture of culture media, reagents and medical devices for ART researchers and clinicians.

In 2009, Irvine Scientific approached
embryologist Dr Matthew ‘Tex’ VerMilyea to help them develop and validate a ‘single step’ embryo culture medium.

"In the early days of our field, scientists were using a very simple one-step system to incubate embryos, but it didn’t work very well," explains VerMilyea, now Vice President of IVF Lab Operations for Ovation Fertility. "Further developments led to a sequential system that used three different media to help grow embryos to the blastocyst stage, about five or six days after fertilization. But this involved extra costs, time, and moving the embryos from one culture to the next. Irvine Scientific decided to go back to the beginning and look for a single-step medium that would have all the necessary components for embryos to grow."

This was around the time when time-lapse photography was introduced to the ART field. "A little camera placed under each embryo took a snapshot every five minutes, providing a really good understanding of how embryos grow and develop," says VerMilyea.

VerMilyea and his team used time-lapse micro-imagery to compare mouse embryos cultured in a variety of media. "And lo and behold, we were able to grow really nice blastocysts using our one-step medium. This led to a huge paradigm shift in the field," he says.

FUJIFILM Irvine Scientific optimized culture media to facilitate the uninterrupted culture of embryos. VerMilyea, who has studied and worked in many countries including the UK, Japan, and New Zealand, says his early work with FUJIFILM Irvine Scientific skyrocketed his career.

He then worked with the company to improve single-step culture media by adjusting the lactate content. This led to the development of new culture media with a low-lactate formulation that reduces the amount of stress on developing embryos.

"Our data shows that more embryos are chromosomally normal when grown in this media compared to higher lactate media," says VerMilyea.

"What I enjoy about working with FUJIFILM Irvine Scientific is that they really rely on individuals in the field like me to bring them ideas from their findings in the actual laboratory," says VerMilyea.

For example, his clinical work led him to suggest a more viscous ‘vitrification’ formula for freezing eggs and embryos. "So FUJIFILM Irvine Scientific adjusted their formulation to meet our needs." He has also suggested the development of a medium that can support the maturation of eggs. This holds potential for people with cancer to freeze more eggs for implanting when they are ready to use them, he explains.

"That kind of interaction is priceless. We have access to the human material and they have access to research and development. They come to us with prototypes and we provide feedback for improvement. That interaction is key, not only to the success of a good laboratory, but also for our patients," says VerMilyea.
LINKING COLOURS TO ILLUMINATE DISEASE MARKERS

An endoscopic system developed by Fujifilm has the potential to transform disease diagnostics by improving image detail.

**“OUR LCI TECHNOLOGY MADE IT EASIER TO IDENTIFY SESSILE SERRATED ADENOMA.”**

An endoscopic system developed by Fujifilm has the potential to transform disease diagnostics by improving image detail.
range — a ‘narrowband’ spectrum — finer details of a previously uniform red area can be uncovered.

Until recently, users would have to insert a filter in front of the white light source in order to isolate light of certain wavelengths and achieve a narrowband spectrum effect. This is not the case in when Fujifilm’s technology is applied to endoscopes.

“Our technologies have dispensed with filters, and instead use a light source created by combining multiple semiconductor light emitters,” says Yasuda. “Altering the respective intensity of these elements can produce not only a broadband spectrum, but also narrowband spectrum light, depending on the observations you want to make.

“Blue Light Imaging (BLI) emits light restricted to a narrowband spectrum of short wavelengths (blue and violet) that are easily absorbed by haemoglobin,” says Yasuda. “This allows users to clearly see the microvascular structures and surface textures in mucosa.”

With Linked Colour Imaging, the image processor takes data from the broadband spectrum and combines it with BLI’s narrowband spectrum. The LCI setting enhances slight differences in mucosa colour caused by inflammation and erosion, increasing the visual distinction of any changes over time.

The resulting images are similar in colour tone to the white light images that doctors are familiar with, but the surface details and blood vessels, together with any abnormalities, can be easier to spot (see image below).

“To give a practical example of LCI application, flat polyps are difficult to detect due to the relatively minor difference in colour compared to normal mucosa,” says Yasuda. “A recent study showed that our LCI technology made it easier to identify sessile serrated adenoma — flat lesions in the colon that can be precursors to cancer.”

The available literature suggests that even a 1% increase in adenoma detection during colonoscopy could result in a 3% decrease in colorectal cancer risk and a 5% decrease in related deaths.

The introduction of LCI is expected to contribute to a decrease in gastrointestinal cancer mortality rates. These technologies may not highlight every visible alteration caused by disease, so the Fujifilm team is working on other narrowband illumination techniques within parts of the light spectrum that are not yet used. With REiLI, Fujifilm’s medical AI technology brand, the team is working towards improving the quality and efficiency of disease detection, by using LCI images as AI training data.

References
FROM TRASH TO TREASURE

Improvements in isolation and purification techniques have broadened the description of the exosome to more than just a cellular garbage collector.

A new exosome isolation kit, developed by FUJIFILM Wako Pure Chemical, could help researchers establish a better understanding of the extracellular vesicles’ many functions.

Exosomes are small, membranous vesicles released from cells, that were originally considered simply as removers of cellular waste. Now, as their roles in cell-cell communication and transportation of useful molecules are being discovered, exosome studies occur in many biology research fields.

To enable these investigations, exosomes must be isolated from samples and purified. Ultracentrifugation has traditionally been the go-to method to isolate exosomes, but it can be inconsistent, and often results in sample contamination which affects the interpretation and validity of results.

The MagCapture Exosome Isolation Kit PS, developed by FUJIFILM Wako Pure Chemical, uses a calcium-dependent phosphatidylserine (PS)-binding protein called Tim4 to avoid these drawbacks.

In the Isolation Kit PS, samples are reacted with magnetic beads immobilizing Tim4 and calcium. Tim4 is bound to a phospholipid called phosphatidylycerine, which is present on exosome surfaces, so any exosomes within the sample bind to the beads. The beads are then separated using magnets. Following this, a chelating agent, called EDTA, is used to remove calcium, so that purified exosomes are eluted from beads under physiological conditions.

“Exosome isolation using this technology can isolate very pure and intact exosomes with less physical damage than those isolated through ultracentrifugation,” says Dr. Takahiro Nishibu, a manager at FUJIFILM Wako Pure Chemical’s Life Science Research Laboratories. He explains that the Isolation Kit PS allows for better reproducibility of results, and that by producing pure and intact exosomes, the technology can enable better studies to deepen understanding of exosome functionality.

FUJIFILM Wako Pure Chemical also produces Tim4-affinity-based analytical assays for the detection and quantification of exosomes and exosome marker antibodies and related reagents, for a range of studies into these increasingly exploitable extracellular messengers. The team has also published two studies1,2 detailing their Tim4-affinity-based technique. “Establishing a greater understanding of exosome functions has the potential for creating an innovative way of treating disease,” says Nishibu, adding that the high biocompatibility of exosomes means they could serve as an attractive drug delivery platform. In addition, exosomes released by certain cancer cells are linked to metastasis, and those released by some stem cells have anti-inflammatory properties — bringing potential for new therapeutics.

References
After more than 80 years of experience using small molecules to develop high-quality photographic technologies, Fujifilm is using that knowledge to manufacture nanosized liposomes for use in drug delivery systems. It has established a new manufacturing site in Japan for liposome formulations, designed to comply with the FDA’s current Good Manufacturing Practice (cGMP) standards, and offers contract development and manufacturing services to third party drug developers.

Liposomes are comprised of lipid bi-layers that form nanostructures that can incorporate active pharmaceutical ingredients (APIs) in their centre. Liposomes are designed to carry drugs through the vascular system, and deliver them to a specific organ or tumour site. Using liposomes as a drug delivery vehicle offers the possibility for reducing the side-effects of drugs, because the liposomes are stable in the blood and less likely to be misdirected to normal tissue in the body, and they are targeted to where they are expected to work well.

“Fujifilm’s liposome development capabilities have evolved from our expertise in the field of silver halide photography, which requires the manufacture and dispersion of small molecules to coat photographic film and paper in a highly uniform, precise manner,” explains Kiyohito Takada, senior manager of the Pharmaceutical Products Division, FUJIFILM Corporation. “We have developed and optimized this process to consistently and reproducibly yield small and homogenously shaped liposomes, which is a critical part of successful liposome manufacturing and important for compliance with Good Manufacturing Practices applicable to pharmaceutical products,” he adds.

To ensure a consistent size and shape of liposomes is imperative to be able to ensure a specific amount of the target API can be stably encapsulated. The liposome’s surface morphology must also be consistent, so that the carrier dispenses correctly and moves smoothly through the vascular system. If the size of the liposome is precisely controlled, it may leave tumour blood vessels which are typically composed of underdeveloped, leaky endothelium.

The company has liposomal formulations of two cancer drugs with undergoing phase I clinical trials in the US. To pursue further potential applications of liposome technology, Fujifilm is collaborating with the National Cancer Center Japan as well as companies and academia engaged in nucleic acid-based treatments. Fujifilm welcomes the opportunity to enter into similar collaborations and to offer contract development and manufacturing services to other organizations and companies whose product development plans can benefit from Fujifilm’s approach to engineering and producing liposome-encapsulated pharmaceuticals.

“We are very proud to be at the forefront of technology that could facilitate ground-breaking therapies,” says Takada. “Our ultimate goal is to provide optimal, state-of-the-art technologies for our collaborators, whilst keeping patients and their treatment at the heart of all we do.”
A REILI GOOD IDEA

Fujifilm’s AI and medical informatics technology initiative, REiLI, will help improve medical imaging, diagnostic support and workflows in clinical settings.

Artificial intelligence (AI) technology developed by Fujifilm aims to improve the speed and accuracy of disease diagnosis and help alleviate the workload of medical professionals.

A 2017 study, published in the *Annals of Family Medicine*, revealed that primary care physicians spend approximately half their time on electronic health record (EHR) data entry.

The growth of medical AI could reduce the time spent by healthcare professionals on EHR, as well as help speed up diagnosis to let medical professionals focus on observing and treating their patients.

"With medical AI platforms we can better support doctors and radiologists with their diagnostic workflow and free up their time," says Fumito Nariyuki, a research manager at FUJIFILM Corporation.

Fujifilm first exhibited integration of its REiLI brand of AI technology with the company’s existing medical imaging, picture archiving, and communication systems (PACS) at the 2018 Radiological Society of North America annual meeting. REiLI combines a range of AI with the aim of facilitating a systematic approach to streamline medical diagnosis and workflow.

Deepak Keshwani, an AI researcher at FUJIFILM Corporation, outlines the comprehensive REiLI technology package. The organ segmentation AI divides medical images into anatomical structures that can be meaningfully analysed, he explains. Then the computer-aided diagnosis AI scans each anatomical structure for abnormal patterns. Finally, the workflow AI utilizes information from the segmentation and CAD AIs to, for example, streamline a radiologist’s workflow by auto-populating a report.

In addition to segmentation of the lungs, heart, kidneys and other abdominal organs, Fujifilm is developing REiLI AI technology that could recognize functional areas of the brain.

"We are segmenting the brain into multiple regions, comparing those images with prior studies, and trying to estimate the rate and direction of brain atrophy," says Nariyuki. “It has potential for drug development in clinical trials, and we hope to eventually use it for diagnostic work, in Alzheimer’s disease, for example.”

Computer-aided diagnosis, such as automated detection of lesions, may help reduce the...
risk of oversight and accelerate the entire process of diagnosis, quantification of findings and treatment. “The number of imaging exams conducted are increasing every year. Our technology will assist with analysing this information for use in a clinician’s diagnosis or decision,” says Nariyuki. “It’s not about replacing doctors, it’s about complementing their work.”

By using AI, detailed, descriptive reports on regions of interest may be automatically generated. From segmentation AI, doctors can get location information; from the computer-assisted diagnosis AI engine, they can get information about characteristics of the region of interest. Combining these results with a form of natural language processing (NLP) that is proprietary to the Fujifilm group, it is possible to generate natural sentences, such as those a radiologist would write, says Nariyuki.

Fujifilm is excited about REiLI’s possibilities, “Currently, our computer-aided diagnosis AI identifies abnormal patterns from images, for instance lung nodules from CT images. We would like to take pattern recognition even further in supporting doctors to identify diseases linked to such patterns and monitor disease progression,” says Keshwani.

Another direction the REiLI team wants to pursue is to use a range of modalities for prediction. This method would be based not only on images, but on information such as blood tests and patient history. “Such a multimodal system would be a great support for doctors,” says Nariyuki.

**CASE STUDY: BETTER TOGETHER**
Fujifilm and Kyoto University have been working together for the past two years to develop AI-based diagnostic support technology focused on improving diagnosis of interstitial pneumonia.

Interstitial pneumonia describes a group of diseases that causes scarring of the lungs, specifically through the thickening and hardening of the lace-like network structure known as the interstitium, which can cause serious breathing problems.

The AI technology under development can identify bronchi, blood vessels, normal lungs and seven types of lesions in the lung fields, and divide the lung fields into twelve zones for quantification, offering a potential way to diagnose diseases earlier and to track disease progression.

Given the rise in respiratory diseases caused by environmental pollution around the world, the REiLI AI diagnostic technology may become increasingly useful¹.

“This novel technology, which can categorize and quantify abnormal opacities found in chest computed tomography (CT) images taken from patients with interstitial pneumonia, has potential for numerous clinical applications. These applications include, but are not limited to: the evaluation of treatment effectiveness, prognosis prediction, and investigation of the pathophysiology of interstitial pneumonia” says Professor Toyohiro Hirai from the Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, who collaborated on the project.

*As noted in the accompanying article, AI diagnostic technology is subject in the United States and other countries to regulation as medical devices. In countries where such regulation is applicable, the AI technology described here would need to be approved before it could be commercialized.*

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**REFERENCES**

t doesn’t look like much, just a thin strip of muscle suspended between two fine wires. Yet this cylindrical shaped piece of cardiac tissue, no bigger than a grain of rice, is a powerful new tool for testing novel heart disease therapies.

Scientists have validated the platform with existing drugs that treat slow heart rates, chest pain, high blood pressure, heart rhythm disorders, and other conditions. Now, more and more companies are turning to this miniature version of the human heart to evaluate experimental medicines before advancing them into clinical trials.

“If you can generate data in translational models such as TARA’s that accurately reflect human biology and physiology early in the development of a drug, that should increase your speed to the market and probability of success,” says Misti Ushio, chief executive of New York-based TARA Biosystems, the company behind the heart-on-a-chip platform, named Biowire II.

The tissues generated on the Biowire II platform are made possible thanks to the unique properties of iCell Cardiomyocytes, a second-generation type of lab-grown heart muscle cell derived from human induced pluripotent stem cells and created by FUJIFILM Cellular Dynamics Inc.

Tens of thousands of these cells — which have been optimized for fast recovery after thawing from cryostorage — self-assemble between two wires positioned just three millimetres apart, yielding a freely suspended 3D tissue. The platform continuously delivers electrical pulses to stimulate muscle contraction bending the wires as the tissue beats.

By measuring the amount of bending in the wires, researchers can determine the force and kinetics of muscle contraction. Changes in calcium concentration and electrical patterns can also be tracked. This comprehensive view of cardiac function provides valuable data on whether or not candidate drugs would affect the mechanical properties of the human heart, which is a key indicator of heart failure.

SCREEN SAVER

Last year, researchers from TARA and GlaxoSmithKline described how heart tissue generated from FUJIFILM Cellular Dynamics cells on the Biowire II platform functioned like real, mature human heart muscle in terms of its contractile response to known pharmacological agents. The muscle tissues generated on the Biowire II platform responded to a range of drugs — both toxic and therapeutic — in ways similar to patients and animal models. The researchers reported the findings in the November 2019 issue of Toxicological Sciences.

According to Ushio, the decision to rely on iCell Cardiomyocytes was strongly market-driven. Owing to the reproducibility and consistency of the product, FUJIFILM Cellular Dynamics’ cells were what drug companies had come to rely upon for their own lab-based drug screens — and as those firms moved into three-dimensional cardiac systems, they wanted to stay with the same reliable cell source.

“Almost every pharmaceutical company we interacted with said, ‘We want to work with you, but we want you to use the FUJIFILM Cellular Dynamics cells, because if you can really recapitulate the biology using these cells that we use every day, that will be meaningful.’”

The proven performance of the cells — with their stable biological profiles and recovery from cryopreservation — also made partnering with FUJIFILM Cellular Dynamics an obvious choice, says Ushio. “Their consistency helps with our consistency,” she says. “It expands what we can do because we have a reliable starting point as a foundation.”

ASSAY DEVELOPMENT

Well over a dozen other companies similarly use FUJIFILM Cellular Dynamics’ cells in their drug-screening assays. For example, at
NanoSurface Biomedical in Seattle, Washington, scientists grow iCell derivatives — either cardiomyocytes or cortical neurons — on finely textured substrates that closely mimic the shape and structure of support tissues in the body. The cells then develop together with the proper alignment and other biophysical properties, allowing researchers to accurately determine whether drug compounds will prove harmful to the brain or heart.

And although the name on the final assay that allows for this kind of predictive drug screening is rarely FUJIFILM Cellular Dynamics, a dedicated team of scientists from the Wisconsin-based Fujifilm subsidiary has usually had a hand in helping partner firms make the most of what iPSC-derived products have to offer.

“People see us as a cell provider, but one of our greatest strengths is in assay development and creating cell analysis platforms that will translate into the clinic,” says Eugenia Jones, vice-president of the life sciences strategy office at FUJIFILM Cellular Dynamics.

Working with iPSCs and their differentiated progeny is not easy. The highly specialized cells require controlled culture conditions for optimal maintenance and performance. Get any of the culturing methods, growth media, or nutrient feeds incorrect and the in vitro platform will no longer accurately reflect in vivo biology.

That is why many academics and companies that focus on drug discovery platforms choose to work with FUJIFILM Cellular Dynamics, notes Jones. Simply put: “We help people work with the cells,” she says.

If any assay providers are interested in using high-quality and reliable iPSCs to accelerate their drug discovery efforts, Jones offers this simple advice: “Come to us if we have the right cell type for you and you want help getting it into a screen faster.”

References
EXPLORING INFECTIOUS DISEASES USING PHOTOGRAPHIC FILM TECHNOLOGY

Applying silver amplification technology could help detect infections missed by conventional testing methods.

Diagnosing infectious diseases could become easier, more rapid, and more accurate, with the use of technology originally used to develop photographs.

Immunochromatography is a simple and rapid diagnostic test that can be performed almost anywhere using a kit with reagents.

For example, to check for common viral infections, a liquid containing a sample swabbed from the patient’s nose is dropped on to a membrane preloaded with relevant antibodies that are tagged with a tiny particle, such as gold.

If the virus is present, the antibodies bind to it. As the liquid flows along the membrane it crosses another line of antibodies on the membrane that react with the virus, trapping the gold-antibody-virus conjugate.

This creates a coloured line on the membrane, indicating the virus is present.

However, the gold nanoparticles are not easy to visually recognize when the particles are few, and consequently the test results are potentially misinterpreted in the early stages of infection when there is only a tiny amount of the virus.

In 2011, in Japan, Fujifilm launched an immunochromatographic infectious disease diagnostic system, that applied silver amplification technology used in the process.

**Mycobacterium tuberculosis**, the bacteria that causes Tuberculosis.
of developing exposed photographic film into black and white photographs.

In this technology, gold nanoparticles catalyse the reduction of silver ions to large silver particles. These large silver particles then subsequently cluster around the gold nanoparticles, and these clusters are significantly easier to visually recognize than the conventional gold nanoparticles.

In 2016, Fujifilm partnered with FIND (Foundation for Innovative New Diagnostics), a Swiss nonprofit organization, and the two are working together to assess the application of this technology to develop a point-of-care test for infectious diseases that can be performed in resource-limited settings in developing countries where stable power supply and trained skillful healthworkers are scarce.

Fujifilm and FIND are committed to continuing with operational research in those countries, with the aim of bringing such a test to real-world clinical settings.

Notes
1. Fujifilm makes no representation that products in this article are commercially available in all countries.
2. The detection kit and the diagnostic system described in this article are not approved by the U.S. Food and Drug Administration.

THE NEXT LINE OF DEFENCE
Fujifilm reagents prevent contaminated products from reaching patients.

Alongside LAL reagents and products, FUJIFILM Wako Pure Chemical also markets their home-grown technology, silkworm larvae plasma (SLP) reagents. While LAL reagents are used to detect gram negative bacterial endotoxin alone, SLP reagents leverage the natural biological defense mechanism of silkworm larvae plasma to detect peptidoglycan that is a component of both gram-negative and gram-positive bacteria and (1→3)-ß-glucan of fungal cell walls with ultra-high sensitivity.

“IT’S THE RESULT OF MORE THAN 30 YEARS OF RESEARCH.”

After LAL tests became commercially available in the 1970s, they reduced the need for animal testing, despite being derived from animal products themselves. Before the LAL gel-clot assay, manufacturers used to test for endotoxins by inoculating rabbits with samples and monitoring their body temperature to see if fever was induced.

Fujifilm are developing reagents based on silkworm larvae plasma.
evolving biopharmaceuticals production

Fujifilm technology has enabled the speedy and efficient manufacturing of monoclonal antibodies.

Many biotechnology companies have turned to mAbs as their biotherapeutic molecular class of choice, because they can be tailored to tackle a wide range of diseases. The efficient and high-quality host cell line and process development is the critical first step in the development of a robust biopharmaceutical manufacturing process. The latest generation of FUJIFILM Diosynth Biotechnologies’ mammalian expression system, Apollo X, may be the key to speed up production of mAbs for clinical trials and beyond.

The Apollo X system, which is capable of delivering industry leading titres, comprises an improved host cell line, proprietary medium, a novel expression vector with a proprietary leader sequence, and streamlined units of operations for efficient process implementation. “With the introduction of Apollo X, recombinant cell lines expressing above 10 g/L in a standard 14 day fed-batch culture can be identified,” says Dr Fay Saunders, Head of Upstream Mammalian Cell Culture at FUJIFILM Diosynth Biotechnologies.

The team at FUJIFILM Diosynth Biotechnologies used a directed evolution approach to derive a population of cells with improved performance, such as good growth and expression capability. “As a contract development and manufacturing organization (CDMO), we needed to create a robust host cell line that can efficiently produce lots of different types of molecules, since we do not know what a client will bring us next to manufacture,” says Saunders.

The properties of Chinese hamster ovary (CHO) cells, the most widely used host cell line for making manufacturing suitable cell lines, can vary enormously within a population and can change depending on their surrounding environment. After spending two and a half years evolving the Apollo X host cell line by continually altering how they cultured the CHO cells, Saunders’ team developed a high titre cell culture process, which has the ability to express a wide variety of molecules, including mAbs.

Refining the growth media — a mix of nutrients including hormones, vitamins and sugars that support cell growth — was a critical step in evolving the initial Apollo expression system, launched in 2014, into Apollo X. This involved repeatedly fine-tuning the media formula and testing each iteration on a wide array of CHO cell lines to confirm it supported the production of different antibody molecules. The researchers then compared the growth and productivity of cells in each media to find which recipe performed best. “This ground-up process allowed us to customize a culture medium for Apollo X cells that requires 40% fewer
Monoclonal antibodies are the basis of many biopharmaceuticals.

components than traditional media,” says Saunders. “The cell line development process uses Cyto-Mine® technology, an instrument that can screen hundreds of thousands of individual cells each day. The integrated microfluidic platform can isolate the desired recombinant cell lines by encapsulating single cells in picodroplets, and, with imaging of these picodroplets, comes the necessary assurance that all of the cell lines originated from a single cell. By utilizing a fluorescent based assay, productivity can also be determined at this early stage. The introduction of this technology has allowed FUJIFILM Diosynth Biotechnologies to reduce its cell line development timeline significantly, down from 25 weeks to 10.

The next generation Apollo X system allows manufacturing ready cell lines to be generated in a shorter period and with higher productivity. However, there is always a desire for continuous improvement and the team is looking at ways to progress the system further.

**INNOVATING CONTINUOUS PRODUCTION PROCESSES**

Monoclonal antibody production — from the upstream processes, such as culturing the mammalian cells that produce them, to the downstream processes such as purifying the final therapeutic target to ensure patient safety — is conducted in batches involving many costly, complex and manually intensive, sequential steps that require great skill and training, as well as occupying a significant clean room facility footprint.

In recent years, continuous production methods — where raw materials are continuously supplied into the process, and products (protein) are continuously produced — have been attracting increasing attention. Throughout
the process, protein and cell waste are collected and removed upstream, and protein is continuously purified downstream, so that degradation, aggregation, alteration, and generation of impurities over time can be suppressed. “The continuous production methods can produce not only higher quality proteins with higher-productivity than batch systems but also proteins that are unstable and difficult to produce in batch production. It may expand the possibilities of biopharmaceuticals,” says Saunders. Production volume can also be flexibly adjusted simply by changing the number of production days to support small volumes of an investigational drug through to commercial production.

FUJIFILM Diosynth Biotechnologies has now created a connected and integrated, all-in-one mAb production assembly line that reduces the associated facility footprint and operational risks, while increasing productivity.

“The therapeutic protein purification process is comprised of multiple sequential steps, with limited advancement in how these steps are conducted over the past 20 years. These complicated processes and operations have made biopharmaceutical development and manufacturing expensive, and innovation in production technology has been eagerly anticipated,” says Dr Jonathan Haigh, Senior Director, Bioprocess Strategy & Development, of FUJIFILM Diosynth Biotechnologies. An ideal production process would be more automated and enclosed so that biomolecules can be generated continuously to intensify process productivity, limiting operational risks associated with complex biomanufacturing. To date, emerging advancements have mostly focused on upstream process science and technology.

Researchers at FUJIFILM Diosynth Biotechnologies, led by Haigh, recently introduced patented, disruptive downstream bioprocessing technology to the biopharmaceutical industry. The technology is able to deliver all required purification process steps into one multi-functional bioprocess machine. Together with advancing bioprocess equipment design, the technology also encompasses advances in on-demand buffer production thereby enabling streamlining protein purification further. The technology was developed by leveraging FUJIFILM Diosynth Biotechnologies’ knowledge and experience in purifying a diverse range of therapeutic molecules, and rationalizing the bioprocessing equipment in its manufacturing facilities into one disruptive, mobile and multi-functional technology platform known as SymphonX.

For the upstream process, Fujifilm has developed its own high-production continuous culture equipment that automatically controls the cell density and nutrients, a system that supplies optimal oxygen, and a suitable medium for continuous culture. By using the Apollo X cell line discussed above, adapted specifically for continuous culturing conditions with custom-formulated cell growth media sourced from FUJIFILM Irvine Scientific, cell density can be increased more than three times that of conventional batch production methods.

“Through our continuous batch strategy and technology, we aim to generate 15 kilograms of purified mAb over a 30-day period, in a facility approximately half the size of equivalent fed-batch facilities,” says Haigh. “Such quantities of antibody, levels of automation, shortened processing time, and intensified facility footprint can only be achieved by harnessing the productivity of our Apollo X cell line, fuelled by FUJIFILM Irvine Scientific media, driven by our connected SymphonX technology and advanced buffer management” he adds.

The company is introducing a 500 litre perfusion bioreactor connected to seven associated and connected SymphonX systems in the UK, and is now offering a continuous production process development service.

Creating innovations in manufacturing technology and processes, such as these, to contribute to advancement of biopharmaceuticals, is the mission of Fujifilm.
OVERCOMING THE GENE THERAPY MANUFACTURING BOTTLENECK

New manufacturing muscle for gene therapy on the horizon.

In the early days of genetic engineering, scientists predicted gene therapies that would treat, or even cure, inherited disease by inserting a healthy gene into a patient’s cells to replace a defective version. After 30 years of continuing improvements, gene therapy appears to be on the cusp of living up to that promise. Today more than 700 gene therapies including gene-modified cell therapies are being developed as potential clinical candidates.
This surge in gene therapy research and development testifies to the rapid evolution of the field since the first clinical trial in 1990 and the first FDA gene therapy approval in 2017.

Progress is undeniable yet there are still significant obstacles to overcome given the complexity of making gene therapies. Specialized technical knowledge in process and analytical development in combination with GMP facilities are essential to bring these therapies to the clinic.

Many gene therapy start-ups and academic laboratories are turning to contract development and manufacturing organizations (CDMO), such as FUJIFILM Diosynth Biotechnologies, in order to access both the technical know-how and facilities.

“If you have a process, the CDMO must be able to transfer that process and establish that the transferred process produces the target viral vector to the desired quality and that the process can be scaled up as it advances in the clinic.” says Michael Baker, Head of Process Development at FUJIFILM Diosynth Biotechnologies.

The company already runs a gene therapy manufacturing facility in College Station, Texas that meets the FDA’s current good manufacturing practices (cGMP) for viral gene therapies. FUJIFILM Diosynth Biotechnologies operates Biosafety level 2 mobile clean rooms that are Biosafety Level 3 capable.

More manufacturing muscle looks to be on the way. FUJIFILM Diosynth Biotechnologies recently invested an extra US$120 million in the gene therapy field, including plans for a 6,000-square-metre Advanced Center for Gene Therapies (ACGT) which will open in late 2021. The new centre will add further process development and analytical capabilities. This investment complements on going work to expand GMP capabilities.

Takatoshi Ishikawa, Executive Vice President and general manager of bioCDMO division, FUJIFILM Corporation says the journey for gene therapy is only just beginning. “There are still many issues to be solved, among them, the lack of plasmid production availability, production efficiency for large scale production and control of manufacturing costs, and also safety and quality. It requires state-of-the-art analytical methods to fully characterize viral vectors in order ensure that they are safe for human use. A large number of scientists have combined their advanced technologies and expertise and are tackling these issues. Fujifilm has a wide variety of technologies from different business fields, and is now working on these challenging goals,” he says.

Many gene therapies are based on the use of a vector to deliver the genetic payload to...
the target location. The vector of choice for most of today’s gene therapies is adeno-associated viruses (AAV) but it is here that the manufacturing bottleneck is particularly acute as an ever increasing amount of AAVs are needed to meet growing clinical and subsequent commercial demands. The most common way of producing recombinant AAV (rAAV) for gene therapy involves simultaneously delivering three different plasmids to the cells. One plasmid, the gene of interest plasmid, codes for the gene of interest, the second, the Rep-Cap, codes for the genes required for replication and capsid assembly, and the third, the helper plasmid contains the Adeno virus helper functions. Compared to antibody production, the efficiency of rAAV production is expected to increase at least 1,000 times.

Michael Baker says once the bottleneck is cleared, gene therapy treatments will really take to the sky. “We constantly work to improve production efficiencies, and to reduce time and effort to provide our customers with their vectors.”

**ONCE THE BOTTLENECK IS CLEARED, GENE THERAPY TREATMENTS WILL REALLY TAKE TO THE SKY.**

He says FUJIFILM Diosynth Biotechnologies is constantly improving the density of culturing cells, culturing period and transfection efficiency. “The improvements we are working on are aimed at making gene therapies a viable treatment option for the mass market, not just the lucky few.”

If FUJIFILM Diosynth Biotechnologies and its counterparts succeed, gene therapies may soon meet the promise they offer.
A world-first system developed by Fujifilm could significantly speed up and reduce the cost of creating leads for finding new pharmaceutical candidates. After two years of development, the technology, dubbed Artificial Intelligence-Amino Acid Mapping, or AI-AAM has finally made it possible to profile the way drug candidates bind to disease-associated receptors and find possible alternative molecules. It should be noted that AI-AAM only needs the structural formula of a known biologically active compound; it does not utilize any information of the 3D structure of a target protein. This is a major breakthrough in an industry where taking a drug from the lab to regulatory approval costs more than US$2.5 billion and takes at least 10 years.

Drug companies may invest vast amounts of money into a potential medication, only for it to fail when untenable toxicity is revealed and efficacy is not demonstrated during pre-clinical or clinical trials. The chance that any molecule makes it from initial testing as a potential medicine to being approved for marketing is as low as 1 in 20,000 to 30,000.

“THE NEW COMPOUNDS MAY EXHIBIT BETTER PROPERTIES THAN THE EXISTING DRUG.”

Artificial intelligence-led drug development will become the major approach in the field, says Mayumi Suzuki, General Manager of the Analysis Technology Center, FUJIFILM Corporation. However, she notes that current AI models are limited by their demand for huge amounts of experimental data such as binding affinity, or the 3D structure of a target protein, or intensive computation. To avoid these problems, she stresses they needed to develop technology that had never existed before.

AI-AAM sidesteps these limitations by optimizing the process of determining how drugs interact with their targets. The technology works by simply taking the chemical structure of a known drug, and calculating its "AAM descriptor," a profile that reflects how the drug binds to 20 different individual amino acids — the building blocks of proteins. Fujifilm scientists have discovered that these profiles are specific to how a drug interacts with a fully-formed 3D protein, such as a target receptor. The team proposed a short-cut to traditional drug discovery. Because the profile represents the binding affinity of the drug candidate to the 3D protein, carrying out 3D protein structural analysis or collecting massive amounts of experimental data for AI learning is no longer necessary. Instead, armed with a drug’s AAM profile, AI-AAM can either search the world’s digital libraries of known compounds for those with a similar profile, or generate new molecular structures that bind to the protein of interest.

At first glance, designing new drugs that serve a similar function may appear to be reinventing the wheel; but Suzuki explains that it’s anything but. “We are testing to see if the new compounds exhibit different properties than the existing drug and if they avoid issues such as drug resistance or side-effects present in the original medication.” AI-AAM may also have the potential to take an unsuccessful candidate, perhaps rejected due to tolerance issues, and turn it into an attractive new medicine.

Current modeling technologies struggle with designing new molecules from scratch, often suggesting drugs that are unstable or unfeasible to synthesize. Suzuki says Fujifilm researchers overcame this issue by collecting the information necessary for stable compounds from the huge number of known compounds in existing chemical libraries, and coding AI-AAM to work within the constraints that produce viable molecules.
Fujifilm’s technology can generate drug candidates from the structural formula of a known biologically active compound without experimental data.
Using AAM descriptors to inform an artificial intelligence model dispenses with the need to generate enormous amounts of experimental data or manually screen compound libraries for potential matches. In addition, calculating AAM descriptors is more than 1,000 times faster than the calculation of a target protein’s 3D structure, used by existing computational-based methods.

The team behind AI-AAM validated their new technology through two studies. In the first, chemical structures were entered into the system for an anti-cancer agent, and for an antibacterial drug. Following this, AAM descriptors were calculated for nearly 11,000 compounds from existing drug databases and, after just a few hours of computation, AI-AAM was able to suggest 14 potential new anticancer drugs and 13 potential new antibacterial drugs from the processed database.

The team then synthesized and tested these new candidates, finding one anti-cancer agent and two antibacterial drug candidates, which provided a success rate of 7% and 15%, respectively. Considering that two stalwarts of drug discovery, high-throughput screening, and docking simulations, have respective success rates of <0.1% and <10%, this indicates that AI-AAM will be a competitive method for designing new pharmaceuticals.

In the second study, researchers provided AI-AAM with the chemical structure of a biologically active molecule and tasked it with the design of new compounds with similar AAM descriptors, and similar pharmacological activity. Within a week, the AI-powered technology derived a wide variety of 33 new candidate pharmaceuticals that could be further investigated and eventually yield a working drug.

Now that AI-AAM has proved its worth, Fujifilm is looking to help drive rapid growth in the industry, through partnering with drug development companies. In addition, Fujifilm is well-placed to develop new medicines in-house and is eager to see the advancements in medical science that AI-AAM can yield. “Since our establishment, Fujifilm has constantly worked on developing technologies that are ahead of the times in a variety of business fields such as photographic films and display materials,” says Suzuki. “Our biggest strength is our wide range of advanced technologies, each of which is supported by a team of excellent technological experts. AI-AAM consists not only of typical methods used in the pharmaceutical field but also of the technologies which have been developed throughout our long history. I believe this is the reason why we succeeded in developing this unique method. By using and improving AI-AAM, we are confident that we will keep creating value in the pharmaceutical industry.”

Clinical trials of investigational treatments for Alzheimer’s disease may benefit from a technology that can accurately predict the probability of developing the neurodegenerative disorder.

An artificial-intelligence system that may help predict the likelihood that a person will progress from mild cognitive impairment to Alzheimer’s disease within a year has been developed by researchers at Fujifilm. This system may thus accelerate research into the devastating disease by making it faster and easier to identify suitable patients for clinical trials of potential treatments.

Alzheimer’s disease and related forms of dementia represent one of the world’s biggest medical problems, with an estimated 50 million sufferers globally and no treatments that can slow or halt its progress. It devastates the lives of sufferers and their families and imposes a huge economic burden on society. The situation is only going to get worse as the global population ages.

Some people who exhibit mild cognitive impairment (MCI) are stable over time, whereas others progress to full-blown Alzheimer’s relatively quickly. “Less than 20% of MCI patients enter into Alzheimer’s disease within a year. If we can predict who will progress into Alzheimer’s disease, the effectiveness of drug candidates can be more accurately evaluated in our clinical trials,” says Toshikazu Ban, Corporate Vice President, Deputy General Manager Pharmaceutical Development.
A ‘heat map’ generated by an artificial-intelligence system for assessing whether people with mild cognitive impairment will develop Alzheimer’s disease within a year. Brain regions coloured red contribute most to the prediction.

The AI technology described in this article is currently used for research and development purposes only and has not been approved by any responsible government agency in any country for diagnostic purposes.

Products Division of FUJIFILM Corporation.

Now, a team at Fujifilm has developed a system that can predict with an accuracy of 86% whether a person with mild cognitive impairment will or will not progress to Alzheimer’s disease within a year — the most accurate reported so far¹.

The Fujifilm system uses artificial intelligence to analyse three kinds of input data: brain images, cognitive tests scores, and conventional medical data.

The system was able to achieve such a high accuracy by adapting image-processing technologies that Fujifilm had previously developed for whole-brain scans. Unlike ImageNet, a dataset containing more than 14 million images that can be used to train object recognition software, the available training dataset here is less than 1,000, comprising medical images of the MCI patients who progress or don’t progress into Alzheimer’s disease with their multimodal medical info including cognitive scores. Despite the limited number of training samples, the system was able to achieve high prediction accuracy thanks to image normalization technologies developed by Fujifilm through its Photographic and Medical Systems businesses.

In addition to its predictive ability, the system can also generate ‘heat maps’ that show which regions in the brain contribute most to the prediction (see image), and in a lot of cases the ‘heat maps’ confirm the regions which neurologists focus on, such as brain ventricles.

So far, the artificial-intelligence system has been trained only using data from the ADNI (Alzheimer’s Disease Neuroimaging Initiative) in the US, but the Fujifilm researchers are now training it with larger, more diverse datasets that include people from a variety of ethnic backgrounds. This will extend its applicability.

The developers of this system anticipate that the technology could be a useful tool for instigating early intervention in Alzheimer’s disease. They also think that it could be extended to other diseases in the future.

References

PROMISING COLLABORATIONS

Fujifilm is working with a number of universities towards the creation of future therapies to combat diseases of the central nervous system, such as Alzheimer’s disease and cardiovascular diseases such as stroke.

For example, through joint research with Dr Rudolph Tanzi of Massachusetts General Hospital, Fujifilm is investigating the link between abnormally activated microglia and the pathogenesis of Alzheimer’s disease, and is looking into the possibility of treating Alzheimer’s disease by adjusting the microglia’s function.

Moreover, with Dr Takuya Takahashi of Yokohama City University, the company is studying synaptic plasticity, which plays an important role in a wide range of neural functions such as learning and memory. The team has achieved an interesting result in an animal model pertaining to the recovery of motor function after stroke¹. “Synaptic physiology research could lead to substantial medical advances through effective collaboration with pharmaceutical companies,” says Takahashi.

If the results of these collaborations with academia are combined with the diagnostic potential of an artificial intelligence system, it is expected that future drug discovery research will be greatly accelerated.

References