

# BUILDING A NETWORK FOR DRUG DISCOVERY IN JAPAN

With its new facility in Osaka, CSL aims to **ACCELERATE ITS DRUG-DEVELOPMENT EFFORTS** through extensive collaboration with Japan's biomedical research community.

## Japan has a long-standing reputation of punching well

above its weight in terms of scientific innovation. "When you look at the number of Nobel Prizes that have gone to Japanese researchers, it's clearly a really exciting and high-performing environment for medical research," says Andrew Nash, chief scientific officer and senior vice president for research at CSL's global headquarters, a multinational pharmaceutical company based in Melbourne, Australia.

CSL now aims to tap into that vibrant scientific culture by building on its presence in Japan with a new facility in Osaka. In the near term,

this move is helping the company extend access to its dozens of biotechnology products to a new population of patients.

CSL also has a much more ambitious vision of collaborative research with Japan's scientific community, bolstering the company's own drug-development efforts, while accelerating the translation of Japanese biomedical research innovations into the clinical marketplace.

## EXPANDING OPERATIONS

With an R&D footprint that spans nine countries, CSL has relied heavily on international partnerships to become one of the world's largest

biotechnology companies.

"We at CSL believe strongly in looking outside our own walls for innovation," says William Mezzanotte, the company's head of research and development and chief medical officer, who is based in King of Prussia, Pennsylvania.

CSL is still only a relative newcomer in R&D in Japan. The company opened an office in Tokyo with a handful of employees almost 10 years ago, but this operation has since rapidly expanded.

"We've grown to more than 50 full-time employees," says Haruo Kitado, CSL's head of R&D for Japan. "And over that time, we have delivered on our promise to patients through the

development of more than ten products and indications and dosage forms."

During this initial phase, the top priority has been to work with regional regulatory authorities such as the Pharmaceuticals and Medical Devices Agency (PMDA) to help CSL bring its existing therapeutics to the Japanese market. For example, a drug developed by the company that inhibits the enzyme C1 esterase won PMDA approval in 2022, offering a new treatment option for Japanese patients with hereditary angioedema — a rare genetic disease that causes painful and debilitating swelling of the face and extremities.

## NEW OPPORTUNITIES

More recently, the company has begun to focus on building its on-the-ground R&D capacity through extensive collaboration with the Japanese academic and commercial research community. These efforts are being coordinated through a new CSL facility at the National Cerebral and Cardiovascular Center (NCCV), a clinical research centre in Osaka focused on circulatory and neurological disorders.

The decision to locate in Osaka was largely informed by ongoing collaborations with NCCV scientists, but Nash also sees a uniquely supportive environment for building out a new research hub. "It's a very high-quality academic environment and



▲ CSL is expanding the research it conducts in Japan.

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▲ A molecule of apolipoprotein AI. CSL is conducting clinical trials into the protein's therapeutic efficacy.

very welcoming of external companies that want to come in and collaborate," he says.

Rare diseases like hereditary angioedema are a primary focus of CSL's drug-discovery efforts, and the company is looking to bolster its clinical testing with cohorts of Japanese patients. This is generally essential for winning drug approval from the Japanese Ministry of Health, Labour and Welfare, and Japanese collaborators recently signed on as part of CSL's ongoing AEGIS II phase 3 clinical trial. "Despite starting a bit late, they have already hit their enrollment target and will thus contribute substantially to the final outcome," Mezzanotte says. This trial is testing the therapeutic efficacy of a protein called apolipoprotein AI, which reduces levels of arterial cholesterol and could help reduce the risk of future heart attack.

But the CSL team also sees exciting opportunities to make headway against diseases that are especially prevalent among the Japanese population. Kitado cites the example of interstitial lung disease, a category of poorly understood and largely untreatable respiratory disorders associated with the formation of scar tissue in the airways. "This condition seems to be more prevalent in Japanese populations, especially when treated with certain anti-cancer drugs," he says. "This may be related to genetic composition of the population, and so we have research going on related to this area and may try to bring Japanese patients into that."

## COLLABORATING WITH JAPANESE RESEARCHERS

The CSL team is also enthusiastic about engaging

with Japanese scientists earlier in the process and partnering on discovery research. Mezzanotte praises the country's robust domestic drug-discovery sector, noting that "five of the ten biggest therapies in pharma history came from Japanese innovators."

Kitado cites the example of pioneering research from Tasuku Honjo's laboratory at Kyoto University that uncovered an important immune regulatory protein called PD-1. Many cancer cells exploit PD-1 to quell the anti-tumour immune response, and breakthroughs by Honjo — who would share the 2018 Nobel Prize in Physiology and Medicine for his achievements — and others paved the way for the development of powerful PD-1-blocking 'checkpoint inhibitor' drugs that can

dramatically improve outcomes for some cancer patients. Today, these drugs are a key component of the oncology pharmacopeia, with sales estimated to reach as much as US\$56 billion globally by 2025.

Such collaborations could also help CSL to build powerful new technical capabilities. In the US, the company has engaged in such a partnership with researchers at the Seattle Children's Research Institute, with the goal of developing methods for genetically reprogramming bone-marrow stem cells to treat a variety of hereditary immunodeficiency disorders. Nash notes that until two or three years ago, cell and gene therapies were not a major area of research at CSL.

"But because of that common interest and desire to bring new types of therapies

to patients, we've been able to relatively quickly establish a really strong relationship that spans from basic research all the way through to plans to commence some clinical programmes," he says.

Nash sees a vibrant cell and gene therapy research community in Japan, and is excited about the prospect of developing collaborations that could leverage those strengths to develop more effective treatments for rare diseases. But there are a range of other technological opportunities that could also prove powerful over the longer term.

For instance, Kitado is enthusiastic about the powerful problem-solving capabilities of quantum computing. "In some areas of quantum computing, Japan is leading the world," he says. "It may not be directly applicable to our discovery research now, but nobody knows how intricately it could be connected to our work in 10 or 15 years."

## CSL RESEARCHERS CAN HELP SHEPHERD DRUG CANDIDATES THROUGH THE COMMERCIAL DEVELOPMENT PROCESS

### NETWORK OF PARTNERS

None of this work will be possible until the company establishes a network of partners on the ground, and this is currently the top priority of the CSL team at NCVC. These offices are not designed to directly support research on-site — Kitado says the company has yet to construct an experimental 'wet lab' there — but are ideally situated for outreach, networking and research planning. "They have



▲ CSL will partner with labs in Japan to help guide potential drugs through the commercialization process.

a strong innovation framework there, and some open innovation labs," says Nash. "We already have collaborators there that have worked on our clinical programmes."

CSL's drug-development efforts generally fall into six major categories: cardiovascular and metabolic disease, respiratory disease, immunology, transplant medicine, hematology and vaccines against viral diseases. This covers a lot of biomedical ground and creates ample opportunity for partnerships. The company is currently reaching out to a variety of Japanese research organizations to access interested experts from these sectors, and Nash also sees opportunities to engage with startups through local hubs and accelerators.

But these efforts will take time. "We need to do it step by step," says Kitado, noting that the company's R&D presence is still relatively new to Japan

and not necessarily a known quantity for many researchers. "The first thing to do is build a network gradually, starting from researchers within the NCVC to let them know the good things we are doing, and then we can gradually spread out that network."

He also notes that CSL's Japanese workforce has grown by more than five-fold over the past nine years, and he believes that the company efforts to engage with the local research community could readily follow a similar growth trajectory.

### A SYMBIOTIC RELATIONSHIP

The success of this effort will also hinge on ensuring that the benefits are broadly distributed among the company's collaborators. On the one hand, this will include the routine, reciprocal sharing of knowledge and skills, but the CSL leadership team also aims to accelerate the evolution of promising discoveries into safe,

effective and commercially viable drugs.

By getting involved at the early stages of research, CSL researchers can help shepherd drug candidates through the commercial development process, which is far too complex, expensive, and labour-intensive for most academic labs to tackle. But this will not simply be a handover from one lab to another — Mezzanotte aims to build meaningful, long-term relationships in which both the struggles and the victories are shared.

"For me, a high-quality partnership is one where both sides remain actively involved. And there is a spirit that we are 'in it together', especially when challenges arise," he says. "And challenges always arise in drug development." ■

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