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Japan's Biotech Ecosystem Could Be Headed For An Upswing

by David Wild

After decades of lackluster start-up innovation despite award-winning science, Japan's government and big pharma players are taking steps to spur biotech growth.

Japanese biopharma companies were once industry leaders. In the 1980s, Japanese companies introduced 29% of all new chemical entities approved by the US Food and Drug Administration. The picture is quite different now: between 2011 and 2020, Japanese companies introduced just 7% of NMEs approved by the FDA.

A number of reasons could explain the decline. For example, in the 1990s and 2000s, while the biotech world moved from small molecule development to biologics, Japan lagged in making that transition. Additionally, the Japanese government prioritized social welfare over commercial innovation, implementing strict drug pricing controls in the 1980s, removing financial incentives for biotech innovation.

Whatever the reasons, Japan's government and industry are now rolling out a number of initiatives to stimulate the sector, hoping that, once again, the country can translate a tradition of strong science to commercial products.

Big Japanese Pharma Fostering Biotech

Japanese big pharmas have been playing an important role in cultivating startups. For example, *Takeda Pharmaceutical Co. Ltd.* launched Shonan iPark in 2018, housed in a former Takeda R&D facility. The facility, which was recently made independent of the pharma company, hosts roughly 150 groups, including 1,700 researchers, offering lab space and office space for non-R&D entities, like governmental organizations and venture capital firms. Tenants have opportunities to connect through various programming and have access to crowd-funding and venture capital opportunities.

The iPark model has proven fruitful. In 2023, tenants formed 2,100 partnerships, in some cases creating new companies, as was the case with Orizura Therapeutics, a startup developing human iPSC-derived pancreatic islet cells for brittle type 1 diabetes. The company recently completed a series B round of JPY3.3bn ($21m) and will be trying to raise more financial interest at the BIO International Convention 2024.

“It’s an initial promising sign of the successful startup ecosystem here,” Toshio Fujimoto, CEO of iPark Institute, which operates Shonan iPark, told *In Vivo*.

Shonan iPark is also building international bridges. It recently signed a memorandum of understanding with the Korea SMEs and Startup Agency to foster collaborations between members in the field of cell and gene therapy, an area both countries have strengths in. (Also see "*Japan’s Largest Biocluster, Korean Ventures To Collaborate For Cell And Gene Therapies*" - Scrip, 22 Oct, 2023.)

Fujimoto, a former Takeda employee, would like small and mid-sized biotechs from outside Japan to build a presence in the country, noting that 72% of new molecular entities approved in the US and EU in 2020 were unapproved in Japan.

“The problem is that small and mid-sized startups cannot afford to include Japan in registrational trials,” noted Fujimoto.

Japanese regulators have historically required a Phase I Japanese study arm for all drug trials and the requirement has created a segment of Japanese companies that focus solely on licensing and filling in the regional research requirements, where SMEs may not have the budget to do so.
However, the Japanese Ministry of Health, Labour and Welfare relaxed that requirement last year, creating a more welcoming environment for ex-Japanese companies. (Also see "*Japan Planning To Expand Phase I Waivers*" - Pink Sheet, 5 Oct, 2023.) While Japanese arms of Phase II and III research are needed for local approval, the proportion of Japanese

Kyoto University’s Scientific Strengths

Kyoto University has an illustrious history when it comes to scientific discoveries. In 1992, Nobel Prize winner Tasuku Honjo of Kyoto University and his team discovered the Programmed Cell Death protein 1 (PD-1). In collaboration with Japanese pharma Ono Pharmaceutical, the university developed what would become Bristol-Myers Squibb’s Opdivo (nivolumab).

Kyoto University is also home to Shinya Yamanaka, a scientist who was honored with a Nobel Prize in 2012 for demonstrating that

study subjects is negotiable, and with positive Phase I data, biotechs may feel more confident spending money on a Japanese arm.

Filling The Funding Gap

One issue that has plagued Japanese startups is the slim size of investments. In 2023, Japanese VC and corporate VC investments in biotech companies were 3% of what they were in the US: $913m vs. $28bn.

"The scale is so small, and it's reflected in the slow speed of drug development in Japan," lamented Fujimoto. "Biotechs here cannot take risks with small investments. Most innovations in Japan come from big pharma, whereas in the US, they are from startups."

A recently-launched joint venture between *Astellas Pharma, Inc.*, Takeda Pharmaceutical Co. Ltd., and Sumitomo Mitsui Banking Corporation (SMBC), is intended to alleviate some of the funding pains of startups conducting early drug discovery work, but the size of that initiative is again modest, totaling $3.9m.

mature cells can be reprogrammed into pluripotent cells. Yamanaka has remained in academia, but Kyoto spun out several companies based on iPS cell technology.

ReproCELL, for example, was founded in 2009 and became the first company globally to launch an iPSC-derived research product, and Heartseed Inc., has Phase I/II trials studying iPSC-derived cardiomyocytes for the treatment of heart failure.

Kyoto University itself took steps to promote the commercialization of its research, in 2008 launching iPS Academia Japan, Inc., a one-stop shop for the university's iPS cell-related intellectual property.

Kyoto University's Center for iPS Cell Research and Application has continued Yamanaka's work, developing hundreds of iPS cell types for various diseases and cell stocks and licensing these for use in clinical trials worldwide.

"The idea is that the joint company will do validation experiments, because the majority of the cause of failure for academic startups is the lack of validation data," said Fujimoto, who is iPark-based JV. "Once the mechanism is validated, based on these validated assets, the joint venture company will form a new company and nurture a seed asset, look for global venture capital funding, and eventually launch in the US."

He expects the JV to perform its first experiments this year, with new companies potentially formed as early as 2025.

At the time of the announcement, SMBC highlighted to *In Vivo*'s sister publication, *Scrip*, that there was a "lack of an ecosystem for pharmaceutical start-ups in Japan when it comes to

growing the seeds of new drugs to commercialize them." (Also see "*Takeda, Astellas Found New JV To Support Japanese Bioventures*" - Scrip, 23 Apr, 2024.)

Astellas has also recently launched a biotech facility in the vein of iPark, in collaboration with the global incubator, BioLabs.

The new Astellas facility is located in Tsukuba, a government-planned "science city" located roughly 56 km northeast of Tokyo and is home to several national research institutes, two universities and over 240 private research facilities.

SakuLab-Tsukuba is located in the Astellas's Tsukuba Research Center and offers tenants access to shared lab equipment and non-confidential consultations with Astellas entrepreneurs-in-residence, as well as networking opportunities.

"We don't have a mature ecosystem in Japan, but there are many good scientists, government support and investment, and the situation is changing," Taro Masunaga, executive vice president, Astellas Discovery Accelerator, told *In Vivo*.
SakuLab-Tsukuba's first tenant is Alpha Fusion, a startup developing Targeted Alpha Therapy (TAT) treatments for refractory cancer patients based on technology created partly at Osaka University.

While other tenants have not been announced, Masunaga is confident they will come. It is "prime time" in the development of the Japanese biotech ecosystem, he said, and, "The most important thing is that people have the mindset to innovate.

Missing Skill Sets in Japan

That is easier said than done in a culture that is risk-averse. Masunaga praised Japan's abundance of scientists, "with very good skill and knowledge," but said fundamental business skillsets are missing.

"It's the mindset, and the business sense and knowledge and also knowing the environment of the life sciences," he told *In Vivo*. "And it's the experience with translational research that's missing."

In the spirit of fostering rapid innovation, SakuLab-Tsukuba leases come in brief two-year terms.

"It's not our intention to have companies stay here for 10 years or 20 years," said Masunaga, noting there are already plans to build a SakuLab location in 2025 in Kansai, where there is also an established life science cluster.

Laura Stevens, senior project manager, business development at BioLabs, emphasized that a

major challenge in moving science along from bench to bedside in Japan is the risk-averse mentality.

“It’s a matter of getting over the hurdle that a startup is high risk and that’s ok, that’s part of the journey for commercializing technology,” Stevens told *In Vivo*. "Things will fail and you will pivot to the next step."

In addition to the SakuLabs-Tsukuba location, BioLabs has other facilities in Japan, including one in Kawasaki, where it has partnered with the Innovation Center of NanoMedicine (ICONM), providing laboratory space to several groups working potentially high-value science, such as mRNA-based therapeutics and supramolecular drug delivery vehicles.

BioLabs also has a memorandum of understanding with Kyoto University to develop acceleration programs and life science incubation facilities for startups in the Kansai region.

Stevens said a lack of funding is a widespread challenge in the Japanese biotech environment, but lauded the Japanese government for “making great strides in creating programs to support startups.”

Government Stepping Up

“METI [the Ministry of Economy, Trade and Industry] is putting a lot of money to try and grow startups and grow biotech in Japan,” Stevens said. “They recognize there’s a lot of great technology there, but it needs to be pushed along.”

The centerpiece of METI's initiatives is the Startup Development Five-year Plan, launched in 2022 with the goal of increasing startup investment 10-fold by 2027 through public-private partnerships. METI hopes to create 100 unicorns and 100,000 startups and, perhaps more ambitiously, it wants to change how startups exit in Japan.

The Five-Year Plan notes that while 90% of startup exits in the US are achieved through M&As, in Japan, 80% of startups choose to go public as their exit strategy.

In March, METI also launched the Japan Innovation Campus in Silicon Valley, in collaboration with University of California – Berkley startup accelerator SkyDeck, to foster connections between Japanese startups and international partners.

And, on the heels of the COVID pandemic, METI also launched a funding program to help with both research and commercialization of new vaccines or therapeutics for infectious diseases, in a VC-matching initiative with local investors. (Also see "*Japan Kicks Off $366m Bioventure Support Program*" - Scrip, 19 Aug, 2022.)

There are programs on the local level too. For example, the Tokyo Metropolitan Government's Blockbuster TOKYO program provides funding for firms working on drug design and medical startups.

Stevens believes the deluge of government support could trigger growth in the biotech ecosystem in Japan in the coming years. However, given that investors in Japan are risk-averse, attracting international investors is key, she said. Being able to attract foreign investors requires Japanese founders to effectively communicate their value proposition.

"It's a question of how do you create those pitch decks that resonate with American VCs versus a Japanese scientific audience," she noted. "Being able to tell that story is challenging for any scientist and entrepreneur."

Working With Small Check Sizes

One biotech that has moved steadily down the path from its office in iPark to imminent public offering on the Tokyo Stock Exchange is *Chordia Therapeutics Inc*. The company was founded in 2017 based on a portfolio of assets licensed from Takeda and is focused on developing its lead oncology assset, CTX-712, a first-in-class, pan-CLK inhibitor.

Being armed with assets from a big pharma and led by a CEO with experience at Takeda made fundraising a smoother endeavor than it would be for a company starting from purely academic roots. However, while one would expect investor confidence to translate to significant funding, the company's Series A totaled only JPY1.2bn ($8m), an amount that is relatively modest compared to many US and European Series A rounds.

"It's a nice amount of fundraising in Japan, but compared to the US, it's very small," CEO Hiroshi Miyake, told *In Vivo*. "Small check sizes are a big limitation, but we need to live with that."

Miyake said his company chose a clinical development strategy based on these financial constraints.

"We found nice efficacy in acute myeloid leukemia and ovarian cancer and wanted to continue Phase II clinical development for both indications, but looking at our fundraising ability, we decided to focus on AML right now," he said.

The company has been a success, but financial realities have impinged on its growth, as have logistical realities specific to Japan.

"There are no high-volume centers for hematological malignancies in Japan, so we're focused on our Phase I/II study in the US," said Miyake.

A Japanese Type Of Ecosystem

Ultimately, while Miyake sees the Japanese biotech ecosystem developing, he does not expect it to become "another Boston, San Francisco or San Diego," despite the richness of science in the country.

"Japan may be able to establish a Japanese type of ecosystem," he said. "For now, we need more players, we need more funding, and we need more success cases."