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From East to West: A Japanese Pharma perspective on establishing a global research capability

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Takeda (http://www.takeda.com) is one of the oldest Pharmaceutical companies in the world and has been the largest Japanese Pharmaceutical company for over a decade. Although many of its operations such as development and marketing have been conducted on a global basis for a number of years, research has historically been focused on in-house activities inside Japan, which have a successful track record in generating pioneer blockbuster drugs. To meet the ever-increasing challenge of maintaining a robust pipeline and a continuous stream of INDs, Takeda has embarked on a program to globalize its internal drug discovery capability through the integration of world-class research entities. We outline the strategies, opportunities and challenges of building a global research network from the perspective of a Japanese Pharmaceutical company.

Historical perspective

Takeda's history stems back to 1781 when Chobei Takeda (Figure 1) opened a shop in Osaka, Japan that sold Japanese and Chinese herbal medicines. From this modest beginning grew a company that began importing Western medicines from 1895 and established an exclusive link with Bayer in 1907. Recognizing the importance of innovation, Takeda built its own research laboratories in 1915, which have steadily grown into a major internal research organization, generating a series of blockbuster drugs. While maintaining its domestic Japanese base, over 40 years ago Takeda embarked on a programme to establish its marketing and later development activities abroad in order to extend its operations beyond Japan. Not only was this necessary to compete successfully with overseas pharmaceutical companies, it also enabled access to new opportunities and expansion into therapeutic areas that were less prevalent amongst the Japanese population. In contrast, during this period its research activities remained exclusively located in Japan and leading technologies were introduced from the outside and fully integrated within the internal research platform. This has been a highly successful strategy, enabling the development of four major, innovative products (Table 1), all discovered by in-house research, and in a different therapeutic category, which is relatively unusual for a major pharmaceutical company. These drugs have made significant contributions to disease management and their associated commercial success has positioned Takeda as a major global pharmaceutical company. Currently, Takeda is actively conducting R&D in four therapeutic areas: life style-related diseases (such as metabolic and CV disease), oncology and urological diseases, central nervous system diseases and gastroenterological diseases.

Despite the growing consolidation of Western pharmaceutical companies through merger and acquisition that started in the past two decades [1], the 'omics' revolution and associated development of high throughput technologies [2] of the 1990s gave rise to an enormous fragmentation of innovative research amongst the biotechnology sector and academic community. As a consequence, a cornucopia of diverse new opportunities and technologies became available that were potentially useful for drug discovery and development. It was clear that no single organization, however large, had the capacity or capability to remain, at the forefront of these largely unproven innovations through internal effort alone [3,4]. To maintain the competitiveness of its research activities, Takeda adopted a strategy to identify the key new technologies and incorporate them within its Japanese research

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TABLE 1

Strategic product portfolio.

Product	Indication	MOA	Global market position	Sales (bn $)[a]
Pioglitazone	Diabetes	PPARγ agonist	1	3.8
Candesartan	Hypertension	Angiotensin II antagonist	3	2.1
Leuprorelin	Prostate cancer	LHRH analogue	1	1.4
Lansoprazole	GERD	Proton pump inhibitor	2	12

[a] 2007 worldwide.

centres. Three approaches were used: strategic technology transfer collaborations, a widespread visiting fellow program and corporate investment. An example of the first approach was the agreement with SmithKlineBeecham in 1996 in genomic research and combinatorial chemistry, where the collaboration resulted in both activities being successfully established in Japan. In addition, Takeda has, for a number of years, supported a visiting researcher program, where Takeda scientists are seconded to academic centres around the world for 1–2 years to build relationships and collaborate with leading scientists in key areas. A particular value to this activity, apart from developing English communication skills, was the ability to learn to work in different scientific environments and introduce new ideas and approaches on their return to Japan.

To enhance further its global reach, in November 2001 Takeda established a new subsidiary company called Takeda Research Investments Inc., TRI, (http://www.tri-takeda.com) to be its corporate venture arm [5]. TRI is located in Palo Alto, California, the heart of the US West Coast biotechnology industry and was the first research function to be situated outside Japan. TRI's mission is to identify early stage companies with promising novel, next generation technology for investment or collaboration. By being physically located in a major biocluster, as well as well-connected to the venture community, it is able to be the 'eyes and ears' of Takeda research and to build up a portfolio of innovation across several therapeutic areas that contribute breakthrough technology and products to the research platform (Table 2). TRI is engaged in making investments with the purpose of building close strategic ties with early stage bioventures. Investment may be in the form of loans or the purchase of equity, with board observation rights as a mandatory feature of investment. The aim is to extend Takeda's own discovery capabilities and reach by providing early access to emerging therapeutic products and technologies. TRI does not engage in collaborations or licensing events directly, but introduces Takeda to these opportunities as they come to fruition. As such, the driver behind TRI's investments is to provide a strategic return to the Takeda research process rather than a direct financial return.

Strategy to build a global research network

Takeda has a clear focus in terms of the discovery and development of novel therapeutics across its core disease areas and a strategy to maximise success based on several key principles. The pace of change was, however, too fast and the diversification of technology too great, such that more radical changes were needed for the internal research base to secure Takeda's leading position. Speci-

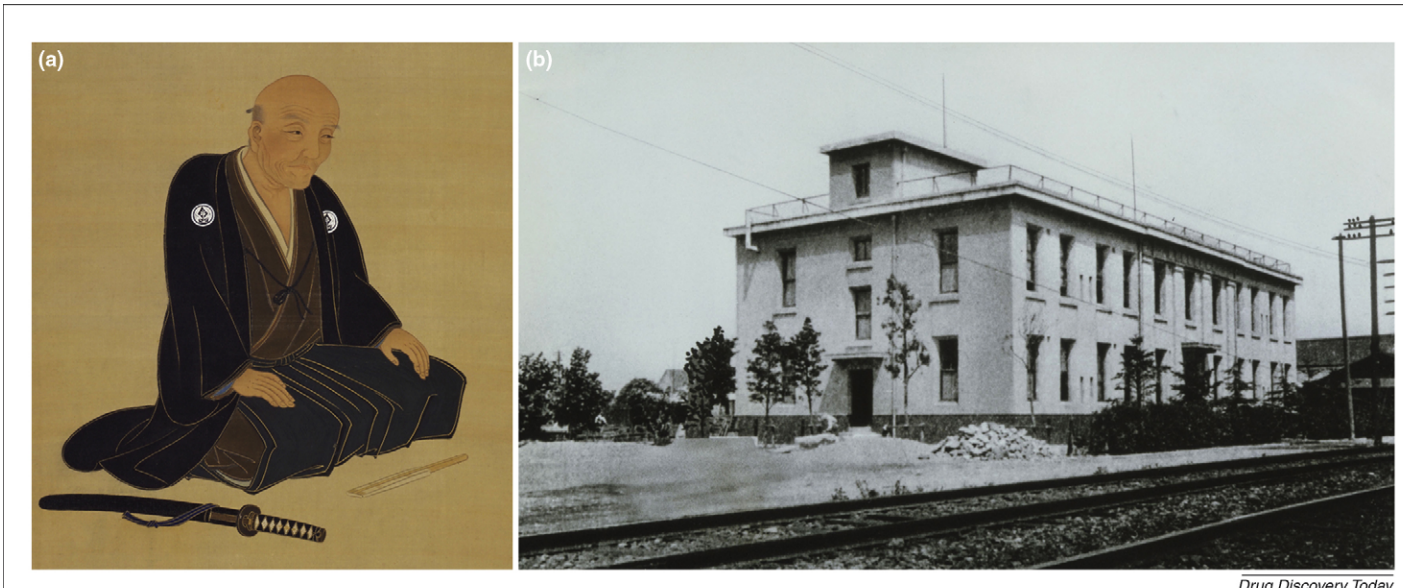

FIGURE 1

Chobei Takeda and the first research laboratory.

TABLE 2

TRI investment portfolio.

Company	Technology	Therapeutic area	Location	Year
Lectus	Ion channel screening	Pain/urology	UK	2004
Serenex	Chemoproteomics platform	Oncology	US	2004
RBLX	Pan-kinase inhibitors	Oncology	US	2004
Adamas	Neurodegeneration	CNS	US	2005
Symphogen	Polyclonal antibodies	Oncology/anti-infectives	Denmark	2006
Xenon	Extreme genetics	Cardiovascular	Canada	2006
Patris	Antibody discovery	Oncology	US	2007
CellCentric	Epigenetics	Epigenetics	UK	2007
Curridium Medica	CNS biomarkers	CNS	UK	2007
Transgeneron	Regenerative medicine	Diabetes	US	2008

fically, Takeda research needed to have a much greater presence outside Japan to participate fully in global innovations as well as additional external R&D activities that complement and extend the overall technology and drug discovery capabilities across the therapeutic areas. Thus, a programme to establish a global research network was started through a combined strategy of overseas IND engines, strategic alliances and academic collaborations as outlined below.

IND engines

Takeda developed a 'buy and build' strategy to establish a number of research centres in major biotechnology hubs throughout the world. These have been designated as centres of excellence in key enabling technologies that have the ability to generate INDs autonomously. Hence, the term 'IND Engine' was coined to describe such centres. While other Pharma companies have regularly used acquisition to obtain key assets and technologies, Takeda, as a Japanese Pharma company, adopted a different perspective with different motivations for acquisition. Most importantly, a key point was to retain the acquired company in its entirety, especially the staff, and to build it up further to be a fully functional IND-generating research centre. Thus, a search was initiated to identify candidate biotech companies that could be successfully incorporated into the Takeda organization. The profile that was desired in potential IND engines included most, if not all, of the following characteristics:

- World class technology complementary to Takeda's own discovery capability.
- Research culture that fits with Takeda.
- Located in a leading 'Biocluster' – ability to be regional research hub.
- Track record or potential to generate INDs.

In 2005, the first such IND engine was established in San Diego, US through the acquisition of Syrrx, a company with premiere high throughput X-ray crystallography technology. The rationale behind this acquisition included a therapeutic focus in metabolic disease and oncology, as well as the product SYR 322, a DPP-4 inhibitor in phase 2 clinical development. Takeda San Diego, TSD, (http://www.takedasd.com) now represents a fully integrated part of the Takeda group with proven IND discovery capability and a powerful technology platform applicable to many target types. This acquisition represented the first establishment of a pre-clinical discovery capability outside of Japan and the location of TSD also provided an opportunity for Takeda to have a presence in a world-renowned biocluster of leading research institutes and companies. This philosophy was central to the building up of new IND capabilities outside of Japan and currently there are three IND engines, whose details are shown in Table 3. The second IND engine to be established was Takeda Cambridge/Takeda Singapore, TCB/TSP (http://takedacam.com), from the acquisition of Paradigm Therapeutics, which is described in detail below. In the case of Takeda San Francisco, TSF (http://takedasf.com), no suitable company with the desired profile in antibody technology was available for acquisition, so it was decided to establish a new research centre *de novo*, since its location in the leading region of antibody therapeutics research of South San Francisco, would enable rapid recruitment of experienced scientists and easy access to key technologies. Although clearly more challenging than incorporating an existing company, it was thought to be the best

TABLE 3

Current IND engines

IND engine	TSD (Takeda San Diego)	TCB/TSP (Takeda Cambridge/Singapore)	TSF (Takeda San Francisco)
Year of incorporation	2005	2007	2008
Proprietary technology	Structural biology	KO mice	Antibody science
Field	Chemistry	Biology	Biologics
Drug target type	Validated	Non-validated	Validated/non-validated
Therapeutic area	Oncology, metabolic disease	CNS, pain, metabolic disease	Oncology, inflammation

BOX 1

Success factors and potential pitfalls for acquisition from a Japanese perspective

Success factor	Potential pitfalls
• Existing collaboration and relationship	• Clear assurance on long-term future/staff retention
• Proven technology	• Not allowing sufficient time for integration to share respective processes
• Location in major biocluster	• Clarity on respective decision making processes & timelines
• Therapeutic area fit	• Unproductive meetings
• Supportive investor base	• Misunderstanding each other's language (correctly interpreting signals for agreement, disagreement and understanding).
• Providing resource to ensure pre-clinical drug discovery critical mass	• Failure to establish clear lines of communication
• Building key relationships after transaction between operational staff (recommend personnel exchanges on both sides)	
• Mutual understanding of autonomy	

option for Takeda to establish an antibody therapeutic capability within the desired 2-year time frame.

IND engine case study: Paradigm Therapeutics to Takeda Cambridge/Takeda Singapore

The acquisition in 2007 of Paradigm Therapeutics provided research bases in Cambridge UK and also, by virtue of Paradigm's wholly held subsidiary, a research presence in Singapore. Paradigm provided a pipeline of novel drug targets identified through its proprietary mouse knockout (KO) approach. This formed the basis for an initial collaboration between the companies in the field of CNS target discovery in 2005. Paradigm's approach had been successful in elucidating the function of several drug targets including the landmark discovery of GPR54, a novel GPCR that plays a pivotal role in regulating the GnRH axis [6] and GPR92, a potential target for the treatment of pain. The approach involves the knockout of specific genes in mice, followed by in-depth phenotyping to characterise and validate potential drug targets. In the case of GPR54, this included collaboration with a clinical group at the Massachusetts General Hospital in Boston, which showed that the function of GPR54 in humans was similar to mouse, essentially acting as the switch for the initiation of puberty. From a therapeutics perspective, modulation of the GnRH axis is important in a number of endocrine and oncology indications. Similar to the case with TSD, key factors in the establishment of Takeda Cambridge included:

- Proprietary technology underpinning pipeline of targets for IND generation.
- Existing collaboration before acquisition.
- Therapeutic fit – CNS, pain, metabolic disease, endocrinology.
- Presence in Cambridge – largest and most significant Biocluster in Europe.
- Singapore subsidiary allowing immediate presence in South East Asia.
- Established scientific network and access to leading academic institutions.
- Availability of scientific talent pool.

The initial CNS collaboration provided Takeda with the opportunity to evaluate fully Paradigm's approach and technology platform in the context of a defined therapeutic area, with a view to its wider application. The collaborative research phase also provided an effective way to establish a good working relationship and provide some insight on compatibility between the companies from a cultural, working and strategic perspective. Most importantly, it provided a vehicle and springboard for exploring a broader relationship that ultimately led to acquisition and integration. Interactions between individuals can be essential factors in any successful deal negotiation and are critical for successful company acquisitions and subsequent integration. This can be especially true when faced with the additional complications of different culture, language and time zone. At the time of acquisition, Paradigm Therapeutics was a private, venture capital-backed company with an international investor base that also needed to support any acquisitive event. A retrospective analysis of why the acquisition and subsequent integration was particularly successful highlights several key areas (see Box 1). Of note is the importance of the open and trusting relationship between senior executives on both sides during the negotiation and integration process, without which the transaction is unlikely to have completed. This relationship had been developed over several years through the initial CNS collaboration deal and the ensuing period and it allowed candid and challenging exchanges, when required, with a climate of trust and openness underpinned by a desire on both sides to conclude the negotiation. From the perspective of Paradigm, the support of the investor base was essential through the entire process and is critical for any company wishing to exit through a similar route.

IND engine operation

With each of the global research centres, the approach that Takeda has taken is to give them a high degree of autonomy for pre-clinical candidate generation, while actively promoting sharing of expertise to provide a balance between ownership and cooperation. Each IND engine is led by a president, who reports to the head of the Pharmaceutical Research Division in Japan. The president retains autonomy over its pre-clinical portfolio and research platform. The IND engines possess chemistry and pharmacology functions that are essential to enable IND generation, although other functions such as toxicology, DMPK and translational medicine can be shared by each IND engine and the Pharmaceutical Research Division (PRD) in Japan which maintains these functions as centres of excellence. The overall strategic focus and goals of each IND engine are determined by mutual agreement between the IND engine and PRD, but operation of the IND engine is left to the IND engine presidents. Thus each IND engine is solely responsible for target selection, project progression and decision-making until a pre-clinical candidate is obtained, at which stage responsibility transfers to the Pharmaceu-

tical Development Division. Also the IND engine president is responsible for resource management and continued development of its own technology platform. Towards the later pre-clinical stages, however, close discussion with Japan is needed to maintain strategic alignment and ensure a smooth progression into development. In some cases joint projects with PRD are conducted, where functions such as chemistry and pharmacology are shared between the IND engine and PRD and there is joint decision making. Earmarked support by the IND engine is provided to the Japanese research groups in areas where the IND engine has breakthrough technology, such a generating crystal structures or knockout animal models. In such cases, annual targets are set by mutual agreement and form part of the IND engines performance goals. Numerous technology transfer/technology sharing activities are conducted by mutual agreement, which are often associated with researcher exchange programmes.

Strategic research alliances

Although the IND engine strategy was pivotal in establishing Takeda's global research network, additional strategic alliances were needed to access key technologies, particularly potentially breakthrough technologies that had not yet progressed to the level of being able to generate an IND. The primary aim of such alliances is to form a long-term relationship with a proven partner to enable technology transfer and collaboration through joint projects to bring the technology to fruition. By focusing on the long-term, we believe there is a greater likelihood for mutual benefits to each alliance partner. A summary of recent alliances is shown in Table 4. Alnylam (http://www.alnylam.com) is a good example of this approach, where strategic alliance with a proven leader will enable Takeda to incorporate state-of-the art RNAi therapeutics technology into drug discovery programmes in metabolic diseases and oncology. The 3-year partnership includes access to RNAi technology and IP, technology transfer to Takeda as well as collaboration on drug discovery for certain targets & delivery technology. It is the first major RNAi therapeutics partnership between US biotech and Japan Pharma company, and also will include 50/50 development and commercialization of Takeda RNAi therapeutic programs in the US.

Academic network

The majority of key innovation opportunities originate directly out of academic research, particularly those related to pathway analysis and target discovery. Partnerships with academia are an essential component of most Pharma companies' research activities [7]. As a long established major pharmaceutical company in Japan, Takeda has naturally developed strong academic links with Japanese universities and government institutes over the years. Far fewer links have, however, been developed with academic groups outside Japan. Although Japanese academia is undoubtedly of the highest level, it was clear that stronger links with worldwide academia are essential to gain broader access to new insights and opportunities in addition to participating more fully in the worldwide academic community. In contrast to the West, Japanese Academia and Pharma have little tradition of physician scientists with skills that cover both basic research and clinical practice. Since bringing overseas scientists with this skill set to work in Japan on a long-term basis is challenging, a major driver for the academic collaborations was to form long-term relationships with physician scientist Principal Investigators. Two major collaborations were started with leading academic institutes, the Beth Israel Deaconess Medical Centre, BIDMC (http://www.bidmc.harvard.edu) in Boston, USA and the Oxford Centre for Diabetes and Metabolic Disease, OCDEM (http://www.ocdem.com) in Oxford, UK. Both partnership are in the area of metabolic diseases and involve collaboration with several Principal Investigators from each institute. The BIDMC collaboration is focused on basic research into novel mechanisms and pathways, enabling Takeda and BIDMC scientists to gain new insights and understandings into disease-causing pathways and importantly identify new drug targets for drug discovery programmes. The OCDEM partnership concerns basic research in a clinical arena, and particularly allows evaluation of pre-clinical candidate compounds in human islets, which provides pre-clinical evidence of POC that is an invaluable tool for project decision-making.

Both these collaborations enable access to unique facilities and capabilities that would otherwise be unavailable to Takeda researchers. In addition, a key feature of each collaboration is a rolling visiting scientist programme, where Takeda researchers are seconded to the academic institute for a year to work in the collaborating PI's laboratory. This provides both valuable training for technology transfer, and greatly enhances scientific exchange and communication between the scientists that continues after the Takeda researcher has returned to Japan.

Different cultures, same goals

Although it may seem obvious to mention the cultural differences between Japan and the West [8], and the unique business and

TABLE 4

Research alliances.

Company	Technology	Therapeutic area	Location	Year
Alnylam	SiRNA	Oncology and metabolic disease	US	2008
Archemix	Aptamer	–	US	2007
LG life sciences		Obesity	Korea	2007
Xoma	Antibody	–	US	2006
Arius	Functional antibodies	Oncology	Canada	2006
Paradigm[a]	Phenotyping	CNS	UK	2005–2007[a]
Lexicon	Target discovery	Hypertension	US	2005–2007
Evotec	Target discovery	Alzheimers	Germany	2003–2007

[a] Acquired and incorporated as IND engine.

working culture in Japan is well documented (for recent examples see [9–11]), the fact that companies still fail to negotiate this barrier and be successful illustrates that its importance needs to be continuously emphasized. This is equally applicable to pharmaceutical R&D. Each approach, of course, has its merits and limitations and the challenge to bring scientists from Japanese and Western companies to work effectively together should not be underestimated. The key to successful integration is basic compatibility and communication. It is for this reason that Takeda is very careful to identify partners whose basic philosophy shared common values with Takeda. In particular, because Japan is a society based on the long-term, the building of lasting relationships is fundamental. It should be remembered that while constant change is a common mantra for many Western Pharma companies, Japan working culture is based on gradual incremental changes driven by proven results. While this may seem conservative and overly risk-averse, in the long run it often proves successful in introducing technologies that make genuine impact on research productivity. The 1990s gave rise to many breakthrough technologies that promised to revolutionize drug discovery, although a decade on, most analysts agree that the promise is largely unfulfilled [2,12,13] There is, however, no doubt that new technology is having a positive impact on drug discovery where it is applied flexibly and linked to an adequate knowledge base [14–16]. Nevertheless, the attrition rate in drug discovery continues to worsen [17] and it is clear that a balance needs to be struck between 'blue-sky' innovation and pragmatism.

Takeda has not been an early adopter of breakthrough technology until a proven application has been demonstrated, as was the case for Syrrx and Paradigm. One of the key functions of TRI is to nurture companies to provide an insight into the probability of breakthrough technologies having practical applications within Takeda. Investigating breakthrough technology requires a high degree of risk taking that is not intrinsic to Japanese business whose traditional strengths have been in producing marketable applications. Takeda's strategy for globalizing its research platform provides a way to access new technology and alternative drug discovery approaches that would be difficult within an entirely Japanese environment. Similarly strengths of the Japanese organization provide a practical focus to the drug discovery programmes of the IND engines. Takeda believes that the establishment of a global research capability, integrating different technologies, approaches and working cultures, presents unique advantages to innovative drug discovery, as well as leading to the scientific and cultural enrichment of its scientists.

Looking ahead

Takeda's products have been based on the strength and innovation of its internal research base and this philosophy is not altered by the construction of a global research network. Concomitant with activities outside Japan, a new research facility is being constructed in Japan to consolidate all the domestic research activities in one state-of-the-art research centre. Because it was not possible to consolidate at either of the existing Osaka and Tsukuba research centres, a new location at Shonan, just outside Yokohama, was selected because it is close to most other Japanese Pharma as well as the major Japanese academic centres. Although relocation will cause inconvenience to researchers in the short-term, the new Japanese research centre will provide the necessary modernization of the current aging laboratory facilities to ensure long-term competitiveness and be the hub of Takeda's global research network (Figure 2) It is unlikely that the process of drug discovery is going to become less challenging or demanding, but by continuing to build and consolidate its global

FIGURE 2

Takeda Global Research Network.

research platform, strategic alliances and academic networks, Takeda believes it will be well placed to face these challenges and identify the opportunities that will generate the next generation of innovative new therapeutics.

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