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EYO, Shiaw Jia

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Shiaw Jia EYO

Abstract

University spinoffs are seen as a potential means of generating wealth through the commercialization of research. Recognizing the significance of university spinoffs, in the late 1990s the Japanese government began to implement changes in legal and policy frameworks to encourage university–industry linkages. Within a decade, the number of Japanese bioventures grew significantly. However, only a handful of successful bioventures remain. This paper seeks to understand the challenges and the real issues hindering the development of university spinoff ventures in the biotechnology industry. Through case study, it examines the history, technology and critical development path of one Japanese bioventure, AnGes MG, Inc.

Introduction

Since the late 1990s, there have been significant developments in Japan's innovation system. With the bursting of the speculative 'bubble economy' and the longest recession in Japan's post-war history that followed it, many of Japan's idiosyncrasies were called into question. In order to deal with the economic crisis, an array of reforms unfolded in Japan. These included increases in the government R&D budgets for basic research, changes in legal and policy frameworks to encourage university-industry linkages, intellectual property reforms and promotion of start-ups such as creation of stock markets for high growth companies and changes in commercial code law.

In May 1998, the Japanese government passed a law to promote the transfer of university technologies as part of its efforts to facilitate university-industry collaboration. This is known as the "Technology Transfer Law", and allows the establishment of Technology Licensing Offices (TLOs), independent of but affiliated with particular universities. The law legitimizes and facilitates transparent, contractual transfers of universities' discoveries to industry. The

number of TLOs increased from 5 to 48 by the end of 2007 (Nikkei Biotechnology 2009). Through the Technology Transfer Law, university-owned inventions can be licensed through TLOs and professors can voluntarily assign their individually-owned inventions to the TLOs.

In April 2000, the "Law to Strengthen Industrial Technology" was implemented. This permits faculty at national universities to work for established private enterprises that aim to commercialize their research efforts. It also eases limitations on outside work so that researchers at national universities can work after hours for a venture business. Faculty members can also take up three years' leave of absence to work in a company to commercialize their discoveries and then return to their previous academic positions. According to Kondo (2009), this law had a significant effect on university spinoffs. University spinoffs increased from 62 in 1999 to 179 in 2003. A fifth of these belonged to life sciences. Nearly 70 percent of the founders of spinoffs were faculty members (Kondo 2009).

In 2001, the Ministry of Economy, Trade and Industry (METI) initiated the Hiranuma Plan, with a goal of establishing 1,000 university-based ventures in three years. METI budgeted approximately $380 million for 2002, $438 million for 2003 and $663 million for 2004 to achieve this goal (Walsh, Baba et al. 2008). By the end of the third year, the Hiranuma Plan succeeded in establishing more than 1,000 university ventures. About 40% of these were related to biotechnology (METI 2008).

As a result of these reforms, within a decade, the number of bioventures grew from a few tens to a few hundreds. The growth was phenomenal, especially between 1998 and 2004, when according to JBA, they grew at an average annual rate of 17%. This was unprecedented for Japan's biotechnology industry. However, on closer inspection, a few disappointing facts remain. The number of newly established bioventures has decreased each year since 2004. In 2008, only 14 were established, compared to 76 new bioventures in both 2001 and 2004. The number of listed bioventures represented only 3.5% of the total number (JBA 2009). Average sales per listed bioventure were approximately $10.8 million in 2008 and $13.4 million in 2009. In addition, most of the sales did not derive from internally developed drugs, but rather R&D support payments from their alliance partners. Based on these facts, this paper argues that the reforms successfully created a large number of small businesses including university spinoffs, but failed to create large, sustainable, competitive companies.

This paper seeks to understand the challenges facing and the real issues hindering the development of university spinoff ventures in the biotechnology industry. The case study used here is AnGes MG, Inc. (hereafter "AnGes"). AnGes is chosen because it was the first

university spinoff in the biotechnology sector to be successfully listed on the Japanese stock exchange. As a listed company, information about financials, drug pipelines, technology, R&D, etc. is publicly available. Secondly, AnGes is the result of the various institutional reforms implemented during the early 2000s to encourage the promotion of university spinoffs. Thirdly, AnGes has been established for more than 10 years, which allows a more detailed and richer analysis compared to other, newer bioventures. This case study draws upon findings from interviews conducted with the CEO of AnGes, Ei Yamada; entrepreneur/founder of AnGes, Ryuichi Morishita; AnGes' investors; annual reports; the company's website; as well as elsewhere.

2. AnGes – History of Establishment

AnGes was established in December 1999 as a university spinoff to pursue drug discovery and development based on gene therapy.[1] Its founder was Ryuichi Morishita (hereafter "Morishita"), an Associate Professor from the Division of Clinical Gene Therapy at Osaka University. Morishita, a graduate of Osaka University Medical School, studied complications related to hypertension such as atherosclerosis (a condition that causes the thickening of the artery walls) in Osaka University. In August 1991, he became a postdoctoral fellow at Stanford University School of Medicine under Victor Dzau. From 1991 to 1994, under Dzau's supervision, he studied vascular diseases, methods to stimulate angiogenesis and gene transfer technologies.[2]

Morishita returned to Osaka University in 1994 and actively pursued gene therapy research. His effort paid back when he discovered a new method to regenerate blood vessels using Hepatocyte Growth Factor (hereafter "HGF") in 1995. His discovery was built upon his accumulated years of experience and expertise in Osaka and Stanford universities. Morishita had chosen HGF gene rather than other growth factor genes because nobody had yet tried using HGF gene for angiogenesis.[3]

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[1] Gene therapy goes one step beyond DNA in making use of the growing knowledge of genomics. In the case of gene therapy, the drug is not a piece of synthetic DNA but an entire gene. The gene is carried through the whole body into the right cells to make therapeutic protein.

[2] Vascular diseases include any condition that affects the circulatory system, such as peripheral artery disease. They range from diseases of arteries, veins and lymph vessels to blood disorders that affect circulation. Angiogenesis is a physiological process involving the growth of new blood vessels from pre-existing vessels.

[3] Prior to Morishita's discovery, research and observation of HGF gene had been conducted with the aim of

Morishita's discovery and techniques were documented in his patent "Medicine Comprising HGF Gene", first filed in Japan in August 1995. In 2001, the patent was granted by the United States Patent and Trademark Office ("USPTO"). After the patent was filed in Japan, Morishita began to publish a series of work in international scientific journals such as *Journal of Hypertension, Circulation, and Gene Therapy*. A search conducted on the Web of Science database using the keywords 'gene therapy' and 'hepatocyte growth factor' showed that Morishita's publications were among the most highly cited. In particular, "Gene therapy inhibiting neointimal vascular lesion", published in February 1995, was cited 544 times by others.

Morishita was convinced that his discovery in gene therapy technology would lead to something useful in pharmaceuticals. Between 1996 and 1998, he approached several large pharmaceutical companies for a joint venture business but his business proposals were rejected on the grounds that his discovery was too recent and therefore too risky for pharmaceuticals companies. Morishita decided to establish a bioventure to commercialize his research. His decision was also influenced by his own experience dealing with biotechnology start-ups during his postdoctoral years at Stanford. In addition, the timing of the establishment of AnGes was right because during the same period Japanese universities lifted restrictions preventing professors from starting their own businesses and encouraged many transfers of university technologies through university spinoffs.

Morishita realized that he needed someone with business experience to run the venture. He was a scientist and was neither keen on nor experienced with the running and managing of a bioventure. He managed to persuade Kensuke Tomita (hereafter "Tomita") to join his new venture.[4] Morishita first met Tomita in 1996 when Tomita consulted him about the potential of HGF gene in generating new blood vessels. During the meeting, Tomita was surprised to find out that Morishita's discovery had not been taken up by any pharmaceutical company.

In December 1999, Morishita, Tomita and Toshikaze Nakamura invested a total of approximately $107,000 of their own money to establish MedGene Bioscience, Inc, later

finding a cure for hepatic or liver diseases. HGF was first confirmed in 1984 as a protein that helps hepatic cells to multiply, by Toshikaze Nakamura, a professor at Osaka University.

[4] Tomita graduated from University of Tokyo in 1974, held a number of positions in pharmaceutical companies such as Sankyo (now Daiichi Sankyo), Eli Lilly Japan, Sandoz Pharmaceuticals, and Rhône-Poulenc Rorer Japan (now Sanofi-Aventis) and RPR Gencell before serving as the first CEO of AnGes. Tomita left AnGes in 2003 and currently is the Chairman of OncoTherapy Science, another listed bioventure in Japan.

renamed AnGes.[5] Shortly after its establishment, Morishita was able to obtain positive pre-clinical data regarding the efficacy of HGF gene in generating blood vessels compared to similar kinds of therapy in the US. He realized that in order for AnGes to be a leader in gene therapy, media exposure was critical. Hence he began to participate in BioJapan, one of the largest industry events for biotechnology in Japan. According to the *Nikkei Weekly*, Morishita made a convincing presentation about the therapeutic potential of HGF genetic drug in treating vascular diseases caused by blockage of blood vessels. Although relatively unknown at that time, AnGes' debut in BioJapan attracted the media's attention and heightened the potential of biotechnology business in Japan (Nikkei Weekly, 2000).

In June 2000, Morishita stepped down and appointed Tomita as CEO of AnGes. According to Morishita, AnGes should be run by a businessman and not a scientist. In November 2000, Morishita managed to persuade another individual, Hitoshi Kotani (hereafter "Kotani") to join AnGes. Morishita met Kotani in 1998 during a gene therapy academic conference organized by Osaka University.[6] Kotani was valuable to AnGes because he had extensive experience with gene therapy.

After assembling his management team, Morishita faced daunting challenges in obtaining funding. Due to the lack of venture capital investment at that time, it was decided that the best way was through an initial public offering (IPO). Masanori Murayama (hereafter "Murayama") was brought in as CEO for the listing preparation. Morishita had met Murayama at a biotech-networking conferences and considered him a good candidate to lead AnGes' IPO because of his rich investment banking experience as well as his personal network. However, a month prior to the IPO, Ei Yamada (hereafter "Yamada") replaced Maruyama as the CEO of AnGes.[7]

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[5] Nakamura is a professor at Osaka University. He was the first to confirm in 1984 that HGF as a protein could help hepatic cells to grow.

[6] Kotani graduated from University of Tokyo School of Agricultural and Life Sciences in 1980. He received his postdoctoral from Cornell Institute of Medical Research in the US. In 1991, he joined Genetic Therapy, Inc., one of the earliest biotechnology companies involved in gene therapy. The scientific founder of Genetic Therapy was French Anderson, also known as the "father of gene therapy." The first gene therapy trial conducted in Japan, at Hokkaido University, also used the gene carrier developed by Genetic Therapy. Source: http://www.amefrec.co.jp/ecolo/056/56_top.html

[7] Some investors raised concerns that AnGes should be led by a CEO with drug R&D experience rather than a CEO with investment banking experience to portray the image of a biotechnology company. Thus in September 2001, the transition of management took place with Yamada being appointed as the CEO, while Murayama was appointed as the CFO. Murayama left AnGes in March, 2003 to establish another bioventure, Y's Therapeutics.

Yamada remains the CEO of AnGes today.

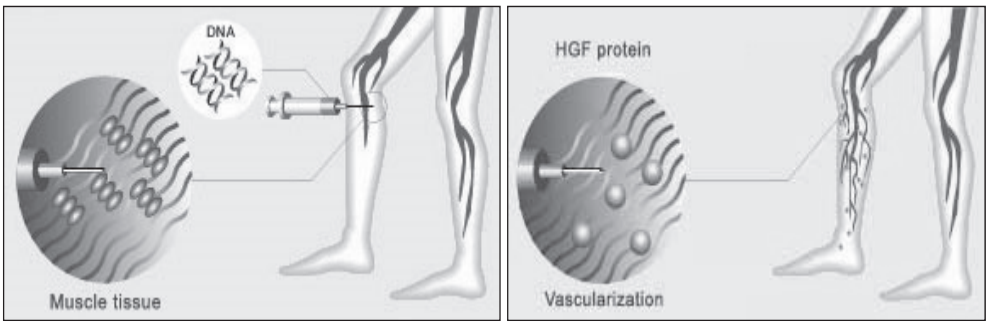
Yamada, who graduated from Tohoku University School of Medicine in 1981, had R&D experience in pharmaceuticals and bioventures through his work at Mitsubishi Chemical, Sosei and Takara Shuzo. From 1982 to 1995, while working for Mitsubishi Chemical, Yamada had the opportunity to deal with Genentech, concerning the licensing of biotechnology drugs. In one of his visits to the US, Yamada was introduced to Morishita, then a postdoctoral fellow at Stanford. The two of them became good friends. After the incorporation of AnGes, Morishita persuaded Yamada to work for AnGes; and in 2001, Yamada joined AnGes.

3. AnGes – Pipelines and Drug Development Process

HGF gene therapy was the main pipeline for the company. AnGes was using HGF gene therapy for two indications or target diseases: Peripheral Arterial Disease (hereafter "PAD") and Ischemic Heart Disease (hereafter "IHD"). Both diseases relate to the blockage of blood circulation, which can lead to pain and tissue damage. PAD is a condition that affects the limbs and IHD is one that affects the heart. HGF can only be injected around the organ's muscles, which explains why it is only used in limb and heart diseases.

For PAD, AnGes was using HGF gene therapy for diabetic patients by providing a treatment of deteriorating blood circulation in limbs (see Figure 1). Patients with severe PAD have their limbs amputated as the last resort to prevent death since there is no other treatment available. According to Yamada, it is estimated that between 10,000 and 20,000 severe diabetic patients a year in Japan are at risk of having their limbs amputated. The statistics are even more alarming in the US, where around 500,000 severe diabetic patients a year are at risk.

Figure 1: HGF Gene Therapy for Peripheral Arterial Disease (PAD)



Before genetic medicine *After genetic medicine*
Source: AnGes' website

One of the challenges of drug discovery and development is the long gestation period. The process of HGF gene therapy for PAD took around 10 years from pre-clinical testing to the drug application stage. As for IHD, nine patients were enrolled for a Phase 1 clinical trials in the US in the late 2005 but no further updates are provided since then. Thus the analysis for this case study is limited to HGF gene therapy for PAD (see Table 2).

As shown in Table 2, the pre-Clinical/proof of concept stage began in Osaka University by Morishita and his team. In late 2000, Morishita obtained positive pre-clinical results and announced his findings in BioJapan. In late 2002, AnGes started preparing for kakunin shinsei (application for confirmation to conduct clinical trials), a process required by the PMDA (Pharmaceuticals and Medical Devices Agency) before an IND (Investigational New Drug). The *kakunin shinsei* process is only required in Japan for biotechnology-based drugs and not for chemical-based drug; the underlying reason is that the former are relatively new in Japan (PMDA 2009).

Table 2: Timeline for HGF gene therapy

Drug development process for HGF genetic drug	**Peripheral Arterial Disease (PAD)**		**Ischemic Heart Disease (IHD)**
	Japanes market	**US market**	**US market**
New Drug Application (NDA) withdrawn	Sep-10		
New Drug Application (NDA) filed	Mar-08		
Phase 3 completed	Jun-07		
Phase 3 started	Mar-05		
Special Protocol Assessment (SPA) obtained	N/A	Nov-09	
Phase 2 completed	Derived from translational research done in Osaka University	Jun-06	
Phase 2 started		Apr-03	
Phase 1 completed		N/A	Nov-05
Phase 1 started			Nov-04
Approval of *kakunin shinsei* or IND approval	Sep-04	Apr-03	Jul-04
IND preparation/ submission	Mar-03	Dec-02	Feb-04
Kakunin Shinsei (Application for confirmation)	Mar-03	N/A	N/A
Pre-Clinical /POC stage	1999 to 2003	1999 to 2003	1999 to 2003

Source: This table is created using AnGes' annual reports, press release and interview data.

It took almost 18 months to get an approval of *kakunin shinsei* from PMDA, because the guidelines for this were often not specifically described, instead depending on the biological source, target disease, site of administration, method of medication, etc. This resulted in many case-by-case consultations with PMDA which further prolonged the investigational process. Yamada recalled that after the submission of kakunin shinsei, PMDA came back with 300

questions regarding HGF gene therapy's protocol.[8]

After obtaining the approval in September 2004, AnGes proceeded with clinical testing. "Translational research" based on clinical research conducted by Morishita was used for Phase 1 and Phase 2 clinical testing.[9] With the translational research results, AnGes was able to advance directly to Phase 3 clinical testing in March 2005. In June 2007, Phase 3 clinical testing was completed in Japan with 40 patients, fewer than the initial proposed number of 120. The difficulty in patient recruitment was the result of a lack of incentives provided for both patients and physicians in Japan.[10]

With positive results obtained from Phase 3 clinical testing, AnGes filed for a NDA (New Drug Application) in March 2008. However in September 2010, after 2.5 years of extensive consultations with PMDA, PMDA concluded that further accumulation of evidence was required for the a NDA approval. AnGes decided to temporarily withdraw the NDA in Japan. According to press release, AnGes planned to resubmit the NDA upon completion of its Phase 3 clinical testing in the US (AnGes 2010).

The withdrawal of the NDA was a disappointment because it further delayed the HGF drug development process. Intense competition means that time is of the essence in the race to commercialize biotechnology drugs. For the development of its HGF gene therapy drug, AnGes faced competition from among others Sanofi Aventis, Genzyme, and Cardium Therapeutics (see Table 3). Even though all of these companies were using different genes and gene carriers/vector, they were all competing in the same target market. As shown in Table 3, AnGes was initially ahead in the process of obtaining a NDA for Japan's market. However, with the rejection from PMDA, AnGes had to wait for its Phase 3 clinical trials in the US, which might take several more years and cost several hundred more million dollars.

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[8] When AnGes submitted for an Investigational New Drug (IND) to the FDA in the US in December 2002, the FDA came back with only 20 inquiries. Within three months, an approval for IND was obtained.

[9] This was an exceptional case in order to obtain more accurate data on the safety and efficacy of HGF gene. Clinical research data conducted by universities are usually not integrated into the clinical testing process unless permission has been obtained. Under the Pharmaceutical Affairs Law ("chiken" in Japanese), the "sponsors" for clinical testing can only be pharmaceutical companies (including bioventures). Clinical testing performed by medical doctors and university researchers is known as clinical research. In addition, the two separate systems do not share a common information database. The separation between clinical research and clinical testing leads to inefficiencies in the drug development process. (Kawakami and Yamane 2007).

[10] This point is also highlighted by Yamada (2005) and Yonekura and Suzuki (2006).

Table 3: Competitors in PAD and IHD Market (as of June 2010)

Company	Gene (Vector)	Indication	Drug Development Process				
			Phase 1	Phase 2	Phase 3	Approval	Market
Anges MG	HGF gene (Plasmid)	PAD (Japan)					
		PAD (U.S.)					
		IHD (U.S.)					
Sanofi-Aventis	FGF - 1 gene (Plasmid)	PAD (Worldwide)					
Cardium Therapeutics	FGF - 4 gene (Adeno virus)	IHD					
Genzyme	HIF - 1a (Adeno Virus)	PAD					

Source: AnGes' homepage, Medtrack database

4. AnGes – University-Industry Linkages

AnGes was a university spinoff from Osaka University. AnGes and Osaka University formed close linkages as evidenced by the analysis of patents and non-patent references (see Table 5 and 6). As of June 2010, according to Derwent Innovation Index database, AnGes had 59 patent families.[11] Based on a search with Japan Patent Office, AnGes filed 62 domestic patents and 17 were granted. Based on a search with USPTO, AnGes filed 26 patent applications and 12 were granted [12] (Table 5).

Table 5 also illustrates that the top five inventors listed in AnGes patents were all affiliated to Osaka University. This indicates that the source of the knowledge indeed came from Osaka University. The research work of some of the inventors, particularly Morishita, was highly recognized, as shown by the high number of patent citations.[13] According to Trajtenberg (1990), high patent citation indicates the significance of technology. In addition, Morishita's work was

[11] Patent family refers to the grouping of related patents and patent publications into a single database record to illustrate the global coverage of the invention.

[12] The number of patents here reflects only patents filed independently by AnGes. Patents filed as a result of joint research are not considered.

[13] Patent citation is the number of times a patent is cited in subsequent patents. For this case, it reflects the total number of patent citation up to June 2010. Patent citations showed in Table 5 is the sum of patent citations associated with the corresponding number of patent family. For example, a total of 112 patent citations for 59 patents which Morishita listed as an inventor.

recognized with 17 awards, including a Young Investigator's Award (Japanese Circulation Society), Young Researcher Award (Japan Atherosclerosis Society) and Harry Goldblatt Award (Council for High Blood Pressure Research).

The findings in Table 5 also suggest the role of AnGes as a mechanism of knowledge transfer from the university. This type of university spinoff role is pointed to by Lynskey (2004). Knowledge from Osaka University was transferred to AnGes in two ways: codified (assignment of patents) and tacit (Morishita's involvement). As a scientific founder, Morishita had been instrumental in providing R&D direction, advice and guidance. The research team in AnGes had benefited by working closely with Morishita and other professors in Osaka University through a number of joint research projects particularly during the early stages of drug discovery and development.

Table 5: AnGes Patent Analysis (as of June 2010)

Pipelines/ Products	Total Patent Familes	Top 5 Inventors (all pipelines)	Number of Patent Families	Share of Patent Families	Patent Citation (count)	Affiliation
All pipelines	59	Ryuichi Morishita	39	66%	112	Osaka University
		Toshio Ogihara	16	27%	77	Osaka University
		Yasufumi Kaneda	12	20%	36	Osaka University
		Mokokuni Aoki	7	12%	14	Osaka University
		Yoshiaki Taniyama	6	10%	6	Osaka University
HGF	Total Patent Familes	Top 3 Inventors (HGF)	# of Patent Family	Share of Patent Families	Patent Citation (count)	Affiliation
	31	Ryuichi Morishita	24	78%	46	Osaka University
		Yasufumi Kaneda	8	26%	14	Osaka University
		Toshio Ogihara	8	26%	16	Osaka University
NFkB Decoy	Total Patent Familes	Top 3 Inventors (NFkB Decoy)	# of Patent Family	Share of Patent Families	Patent Citation (count)	Affiliation
	21	Ryuichi Morishita	15	71%	62	Osaka University
		Toshio Ogihara	8	38%	48	Osaka University
		Mokokuni Aoki	6	29%	17	Osaka University
HVJ-Envelope	Total Patent Familes	Top 3 Inventors (HVJ-Envelope)	# of Patent Family	Share of Patent Families	Patent Citation (count)	Affiliation
	9	Ryuichi Morishita	6	67%	20	Osaka University
		Yasufumi Kaneda	4	45%	18	Osaka University
		Mokokuni Aoki	2	22%	6	Osaka University

Source: This table is created using data from Derwent Innovation Index.

Another indication of collaboration between university and industry is the extent of science linkage. Research conducted by Narin, et al. (1997) and Tamada, et al. (2004) has

suggested that technologies for the application of biotechnology in drugs and medicine are closer to basic science than are the equivalents in other fields such as chemistry, electronics and manufacturing. Thus it follows that companies with high science linkage patents tend to be closely linked to universities because universities are the providers of basic science.

In order to analyze the extent of science linkage, non-patent references (NPR) such as scientific journals cited in AnGes' issued patents were selected. Based on Narin's methodology of using NPR, a similar type of analysis is conducted. Specifically, the NPR cited by patent examiner on the front pages of the issued USPTO patents is used. AnGes scores an average scientific citation number of 5.58 based on the 12 USPTO issued patents (see Table 6). Narin's research showed that in 1995, the average number of scientific citations per drug and medicine patent for Japan was 3.26 (Narin, et al. 1997). Despite the small sample size, the high science linkage score demonstrated that AnGes and Osaka University collaborated closely with one another.

Table 6: AnGes Science Linkage (as of June 2010)

Patent No	Issued Date	Filing Date	Title	NPR cited by applicant	NPR cited by examiner	Assignee
US 6936594	30-Aug-05	18-Sep-00	Gene therapy for cerebrovascular disorders	15	12	Ryuichi Morishita AnGes MG
US 6989374	24-Jan-06	5-Oct-00	Gene therapy for cardiomyopathy	44	5	AnGes MG
US 7247620	24-Jul-07	9-May-02	Method of treating skin wounds with vectors encoding hepatocyte growth factor	33	21	AnGes MG
US 7259149	21-Aug-07	2-Dec-03	Methods for treating or preventing angiogenesis-dependent symptoms	11	4	AnGes MG
US 6913923	9-Oct-07	14-Apr-04	Virus envelope vector for gene transfer	9	7	AnGes MG
US 7285540	23-Oct-07	9-Jul-03	Medicament comprising HGF gene	45	4	AnGes MG
US 7345158	18-Mar-08	25-Mar-03	Actin related cytoskeletal protein "LACS"	9	3	AnGes MG
US 7427395	23-Sep-08	29-Oct-03	Chemotherapeutic agent-incorporated pharmaceutical	11	1	Genomidea Anges MG
US 7504098	17-Mar-09	25-Feb-05	Method for introducing a biological molecule using a viral envelope	17	1	AnGes MG
US 7585848	8-Sep-09	11-Jan-05	Methods and compositions for treating, inhibiting and reversing disorders of the intervertebral disc	45	3	Rush University Medical Center AnGes MG
US 7595301	29-Sep-09	29-Sep-04	Staple type oligonucleotide and drug comprising the same	11	4	AnGes MG
US 7524830	28-Apr-09	12-Oct-06	Decoy-containing pharmaceutical compositions and method of using the same	18	2	AnGes MG
US 7790692	7-Sep-10	31-Mar-05	Hepatocyte growth factor nucleic acid sequence to enhance musculocutaneous	17	3	AnGes MG
Average NPR (Non Patent Reference)				21.9	**5.34**	

Source: This table is created using data from USPTO database.

5. AnGes – Funding

As a drug discovery and development bioventure, AnGes required substantial and persistent funding for its R&D expenses. It spent an average of approximately $28 million a year on R&D,[14] its highest expenditure item. The R&D intensity (R&D expense over sales) was more than 100% for most years. The second highest expenditure was the salary of the employees.

[14] This is based on average R&D expenses from 2001 to 2009. See Table 7.

As of December 2009, AnGes had 80 employees and the total salary expense was $7.8 million. The average monthly burn rate from 2001 to 2009 was approximately $2.8 million (see Table 7).[15] In other words, for every month in these nine years the company spent an average of $2.8 million to conduct its operation.

Table 7: AnGes Total Operating Expenses (2012–2009)

	Amount (in million yen)								
Year	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**
Sales	1,300	1,794	2,453	2,696	2,430	2,912	1,720	951	586
R&D Expenses	745	1,726	2,807	3,679	3,791	3,852	3,147	2,911	2,350
R&D Intensity (R&D/Sales)	57%	96%	114%	136%	156%	132%	183%	306%	401%
Selling, general and administrative (SGA) (incl salary)	291	582	593	578	610	583	613	675	779
Total Operating Expenses (R&D +SGA)	1,036	2,308	3,400	4,257	4,401	4,435	3,760	3,586	3,129
Burn rate (amount per month)	86	192	283	355	367	370	313	299	261

See footnote[16] . Sources: AnGes 2002, 2003, 2004, 2005, 2006, 2007, 2008, 2009a

In order to afford this, access to funding was critical. The earliest funding of $107,000 came from the founders. The company did not receive any funding from angel investors, Small Business Innovation Research (SBIR) grants from the government, or from venture capital investors.[17] The main reason was the limited supply of venture capital funds in Japan. In 1999 for example, only 3.6% of Japanese venture capital fund investment was in biotechnology. Many of the Japanese venture capital firms were risk-averse to the idea of investing in bioventures at that time because biotechnology was relatively unknown. At that time, there was no precedent for any form of exits such as IPO, acquisition or trade sale in biotechnology investments.

[15] Burn rate is the rate at which a new company uses up its cash resources or capital before producing a positive cash flow. The burn rate is usually expressed as the amount of capital used per month or average monthly operating expense.

[16] Sales here are not actual product sales but up-front contract fees, milestone fees, and R&D support payments which AnGes received from Daiichi Sankyo and are considered as revenues in AnGes financial statements.

[17] The only exception was a $300,000 funding from BioFrontier Partners. BioFrontier Partners is an independent boutique venture capital firm focused on life science companies. The company was set up in March, 1999 and led by Yoshihiro Otaki. AnGes was BioFrontier Partners' first investment.

With limited access to venture capital funding, AnGes decided to seek funding through public equity via an IPO in late 2001. Nomura Securities was engaged to prepare for the listing exercise. The world's financial market at that time was bearish following the 9/11 terrorist attack. Despite uncertainty in the financial market, AnGes continued with its listing exercise because its cash was running low. Yamada says:

> "We knew that the financial market at that time was not going to be favorable for the listing but we needed to find some ways to get capital for our R&D and for further development of HGF genetic drugs. If we had missed this listing opportunity, we might not have had the chance to survive…" (Excerpt from interview with Ei Yamada, CEO of AnGes)

Nomura Securities managed to raise $13 million of private placement for AnGes prior to its IPO. Seventy percent of the investment came from Japanese venture capital firms such as Fuji Capital, Daiwa Capital, Aozora Investment, Nomura Securities and Asahi Insurance Capital, and the remaining 30% from pharmaceutical companies such as Ishihara Sankyo and Daiichi Sankyo (*Nihon Keizai* 2001).

The listing of AnGes was highly anticipated because it was the first listing of a bioventure spinoff from a Japanese university. A month prior to its listing, *Nikkei Financial Daily* (8 August, 2002) wrote:

> "Most market participants are focusing their attention on the Mothers market debut of AnGes MG Inc (4563) on September 25 because it will be the first IPO in the field of genomic drugs. In the US, about 80 biotechnology companies have launched their IPOs since 1998, while Japan's stock markets for start-ups were dominated by Internet and service sector companies. AnGes MG's debut, however will change that and provide an opportunity of Japan's biotech field to become a market stalwart."

On 25 September, 2002, AnGes was listed on the Mothers stock exchange (part of Tokyo Stock Exchange). The IPO provided a funding of approximately $35 million. The listing of AnGes made headlines in many major business newspapers. For example, a national newspaper reported the following, "The stock of AnGes MG Inc (4563) fetched an opening price of ¥400,000, some 82% above the initial public offering price of ¥220,000" (*Nihon Keizai* 2002).

Much of the excitement has to do with AnGes being the first "university-based bioventure" to be listed (*Nikkei Industrial Daily* 2002). In addition, the listing of AnGes occurred during a period of "venture boom" in Japan. AnGes' IPO success, as described by

major financial newspapers, spurred the emergence of more bioventures and encouraged the existing bioventures to seek similar listing route.

Although the IPO listing provided AnGes with approximately $35 million, the funding did not last long because of its high R&D expenses. For the year 2003 alone these were approximately $24 million. One year after its listing, in October 2003, AnGes sought follow-on funding from the market by issuing new shares. These raised approximately $58 million. *Nikkei Financial Daily* commented that AnGes' move was timely because there was a growing "biotech bubble" due to enthusiasm and interest from the stock market. Five more bioventures were newly listed in 2003 (Nikkei Financial Daily 2003).

By late 2006, funding was running low again because AnGes' research had entered clinical development trials both in the US and in Japan. With no other available funding options, on March 2007, AnGes raised its third round of funding from the public equity and obtained approximately $73 million. The demand for AnGes' shares was driven by two main factors. Firstly, AnGes' pipelines were making significant progress. For example, HGF gene therapy for PAD had completed initial early rounds of its Phase 2 clinical trial in the US. Secondly, there were positive sentiments from the Japanese stock markets, experiencing a rally at that time due to signs of improvement in the overall economy (Schaede 2008). AnGes was fortunate to obtain its public equity funding before the window of funding closed. A few months later, news about the US subprime crisis came into play and the stock market turned bearish. Nine other bioventures that went for IPO from August 2007 to December 2009 could only procure an average of $10 million.[18]

The second source of funding for AnGes came from its alliance with Daiichi Sankyo.[19] AnGes received a one-time upfront payment plus clinical development support payment by milestones. In return, Daiichi Sankyo obtained exclusive rights to distribute and market HGF gene therapy in Japan after its approval (AnGes 2001; *Nikkei Industrial Daily* 2002). In April 2002, Daiichi Sankyo extended the partnership to include the development of HGF gene therapy in the US and Europe. However in February 2009, "as a result of reassessment of their

[18] Bioventures that went for IPO after August 2007 were GNI, Japan Tissue Engineering (J-Tec), NanoCarrier, Carna Bioscience, R-Tech Ueno, JCL Bioassay, Tella, CanBas and D.Western Therapeutics's Institutes.

[19] In 2005, Daiichi Pharmaceuticals Co., Ltd. merged with Sankyo Co., Ltd. to form Daiichi Sankyo Company Limited. In this chapter we refer Daiichi Pharmaceuticals as the merged entity, "Daiichi Sankyo".

development portfolio," Daiichi Sankyo terminated the licensing agreement involving HGF gene therapy development in the US and Europe. It continued to maintain the licensing and marketing agreement in HGF gene therapy for Japan (AnGes 2009). This was a major setback because AnGes relied heavily on Daiichi Sankyo for part of its R&D funding. AnGes obtained a total of approximately $116 million from Daiichi Sankyo in the form of contract fees and milestone fees from 2002 to 2009. The R&D support payment was recorded under "Sales" in the company's financial statements.

6. AnGes – Stock Performance and Market Capitalization

AnGes experienced a phenomenal surge in its stock performance and market capitalization during its first year of IPO sSee Figure 2 and 3). Market capitalization went up to almost $700 million in less than six months after its IPO although the underlying business did not change much. AnGes did not even have any Phase 2 pipelines at the time of IPO yet the market capitalization for AnGes nearly doubled the average market capitalization of bigger and more established biotechnology companies in the US.[20]

This inflated market capitalization was due to biotechnology "hype". Once the hype and venture capitalists' locked-up period were over, investors began to sell AnGes shares, which resulted in falling share prices and market capitalization after 2003. AnGes' stock performance and market capitalization continued to decline sharply after late 2007 as a result of delays in its milestones and negative pessimism in the overall stock market.

[20] Average market capitalization of sixteen biotechnology IPOs in the US between October 2003 and April 2004 was US$350 million (Kneller 2007b). In contrast, AnGes' market capitalization at IPO was approximately US$400 million and within a year doubled to almost US$800 million.

Figure 2: AnGes Stock Performance (2002–2010)

Source: http://stocks.finance.yahoo.co.jp

Figure 3: AnGes Market Capitalization (2002–2010)

Source: Bloomberg, Japan.

In a span of three years from 2007 to 2010, AnGes' stock lost more than 75% of its value, from ¥609,000 in January 2007 to ¥139,300 in January 2010. The stock price in January 2010 was almost half the value of its offering IPO price set at ¥220,000. *Nikkei Business Daily* reported that investors were losing confidence in AnGes following its failure to market HGF gene therapy by 2005, which it had pledged to do upon its listing (*Nikkei Business Daily* 2008).

There is another reason why AnGes' stock performance was so volatile. AnGes did not have enough institutional investors. An analysis of its shareholding structure at the end of 2009 revealed that 85% of its shares were held by individual investors with Morishita as the largest single shareholder, with 7.14% (see Table 8).

The downside of having individual investors is that stock prices are subject to greater volatility because individual investors are vulnerable to dips in consumers' disposable income and declines in the stock market. Particularly during "down markets", individual investors tend to dump risky stocks in favor of cash or more stable stocks.

Table 8: AnGes' Shareholding Structure

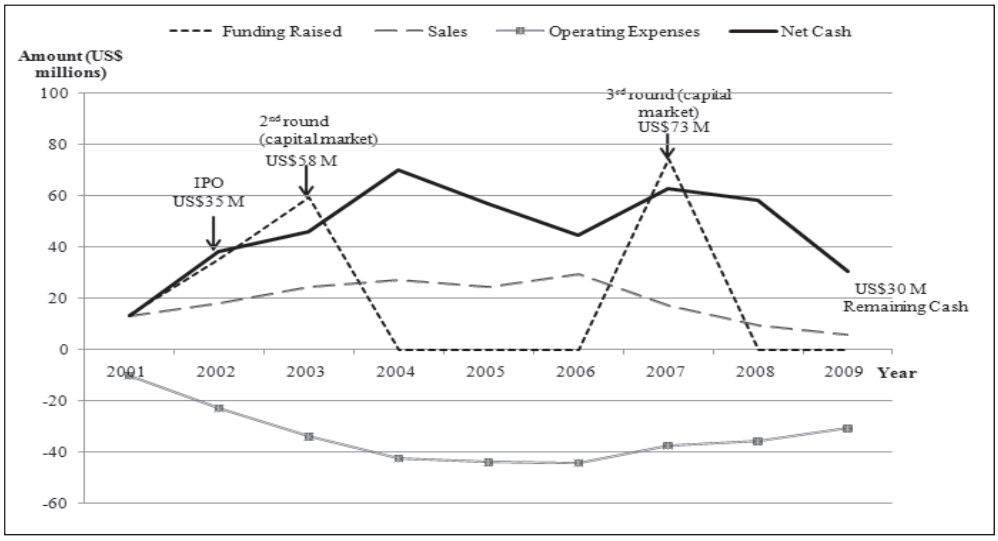
Type of Investors	Number of investors	Number of shares held	% Shareholding
Financial institutions	8	1,134	0.96%
Securities corporations	19	1,832	1.55%
Other corporations	192	12,410	10.52%
Foreign corporations and others	43	2,592	2.20%
Individuals and others	18,823	100,023	84.77%
Total	19,094	117,991	100%

Source: AnGes 2009

7. AnGes – Financial Dilemma

At the end of December 2009, AnGes was left with approximately $30 million (see Table 9), the lowest level since its IPO in 2002. It risked "valley of death," a funding shortage during the development period leading to commercialization. In the worst scenario, the firm fails because it does not have enough funding to sustain its operation. AnGes' cash flow is illustrated schematically in Figure 4.

Figure 4: AnGes Cash Flow Diagram



Source: AnGes 2002, 2003, 2004, 2005, 2006, 2007, 2008, 2009a

AnGes' cash flow signals that the management had daunting financial challenges ahead. With limited amount of cash remaining AnGes has to manage its cash wisely or raised another round of funding. The first option requires AnGes to prioritize its R&D which means putting all of its resources on the most promising pipeline. This is a big gamble since only 0.02% of compounds at the early stage of research successfully reach the market (DiMasi 1995). The second option, fund raising, might not look too promising for now. With the recent declines in AnGes' stock performance and market capitalization, it will be difficult for it to raise another round of follow-on funding from the market. Faced with the current financial dilemmas, AnGes has to come up with more innovative solutions in order to survive.

Table 9: AnGes Statement of Cash Flow [21] (2001–2009)

	Amount (in million yen)								
Year	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**
Cash Flow from Operating Activities	165	-731	-689	-1,433	-1,686	-898	-1,976	-1,978	-2,225
Cash Flow from Investing Activities	-222	-241	-4,484	2,962	-336	-703	-3,668	1,526	-530
Cash Flow from Financing Activities	1,339	3,506	5,927	899	688	395	7,446	29	11
Net increase (decrease) in cash and cash equivalents	1,282	2,534	754	2,428	-1,334	-1,206	1,802	-423	-2,750
Cash and cash equivalents at the beginning of period	17	1,299	3,833	4,587	7,015	5,681	4,475	6,276	5,799
Cash and cash equivalents at the end of period	1,299	3,833	4,587	7,015	5,681	4,475	6,276	5,799	3,049

Source: AnGes 2002, 2003, 2004, 2005, 2006, 2007, 2008, 2009a

8. Discussion and Conclusion

This case study highlights the challenges of a university spinoff in the biotechnology industry. AnGes was created in the late 1990s, motivated by a series of institutional reforms in Japan to spur the development of start-ups. It remains a relatively small company (in terms of number of pipelines, alliances, sales and market capitalization) despite being in operation for so many years. In order to identify the real factor hindering its development, this case study has analyzed some of the factors that drive the growth of bioventures, namely academic entrepreneurship, experienced managers, technology, intellectual property, university–industry linkages, an efficient drug regulatory system and sustainable funding. All of these are present in AnGes except for an efficient drug regulatory system and sustainable funding.

Moritshita displayed the characteristics and qualities of an academic entrepreneur. He took the risk to establish a bioventure to commercialize his own research discoveries. He was also responsible for the recruitment of experienced managers such as Tomita, Murayama and Yamada, and the initial fund raising process. AnGes was led by experienced managers. All of the CEOs had extensive working experience in the industry. AnGes possessed good

[21] Cash flow from operating activities refer to the amount of cash AnGes generates (in this case, payment from Daiichi) minus R&D and other operating expenses. Negative cash flow from operating activities shows that R&D expenses exceed the proceeds from operation. Cash flow from investing activities show AnGes' investment of its surplus of cash. Cash flow from financing activities refer to inflow of cash from investors (in this case IPO proceeds and two rounds of follow-on funding from capital market).

technology seeds from Osaka University. The technology in AnGes was highly recognized, as shown by the patent analysis and non-patent references. In addition, alliance with Daiichi Sankyo for the development of HGF gene therapy also provided legitimacy to the potential of AnGes' technology. AnGes also demonstrated strong university-industry linkages. The company maintained close collaboration with Osaka University through a number of research collaborations and joint patent filings.

In terms of Japanese drug regulatory system, AnGes experienced the following issues. First, a difficulty in recruiting patients for clinical trials due to the lack of incentives for both patients and physicians. According to Yonekura and Suzuki (2006), Japan has about a quarter to a third number of reviewers compared to the US. In recent years, the number of reviewers has increased; but compared to other developed countries, a huge gap still exists. For example as of April 1, 2009, PMDA has a total of 521 full-time employees of whom 346 were 'Review Staff' and 82 were 'Safety Staff' (PMDA 2009). Compared to the US, the FDA had 1,300 reviewers in the Center for Drug Evaluation and Research, which regulates new pharmaceuticals approval. Secondly, a longer approval time for biotechnology drugs due to the lack of qualified reviewers in the area of biopharmaceuticals. This was evident by AnGes' experience in getting a kakunin shinsei and a NDA from PMDA.

Finally, the most critical factor for AnGes is funding. In terms of funding, AnGes experienced various issues as explained below. The lack of alternative funding institutions such as angel investment and SBIR funding forced AnGes to rely solely on venture capital and IPO funding. AnGes obtained no venture capital funding during its formation years. It received this only during the later stage – a year prior to IPO. Such funding cannot be considered as true venture capital funding, where investment is targeted to support high risk, high growth ventures. Rather, it is private placement, where investment is targeted at pre-IPO companies with the goal of making short term capital gains. AnGes' IPO was deemed too early or "premature". At the time of AnGes' IPO, most of its pipelines were still in the early stages of R&D. This is another reason why AnGes repeatedly sought many rounds of funding after its IPO. In contrast, most biotechnology start-ups in the US have angel investments and/or series of venture capital funding before staging an IPO (Robbins-Roth 2000). Even though, AnGes was fortunate to obtain a total of approximately $166 million from its IPO and two rounds of follow-on funding from the equity market, this is only a fraction of the total cost of drug

development (Robbins-Roth 2000; DiMasi, Hansen et al. 2003).[22]

This case study highlights that by falling to provide adequate reforms in Japan's funding institutions such as venture capital, the government may succeed in creating a large number of university spinoffs but failed to nurture these ventures into large, sustainable, competitive companies. The venture capital model in Japan is still largely risk-averse and tends to focus on late-stage investments with the aim of obtaining short-term capital gains. In Japan, the main investors for venture capital are still mainly made up of banks' subsidiaries, investment security houses and insurance companies. Contributions from pension funds remain small, amounting to less than 3% of the total venture capital funding from 2001 to 2008 (JVCA 2009). This is a big contrast to the US, where pension funds are the biggest investors averaging about 35 to 40% of the total venture capital funding (NVCA 2010). According to *Wall Street Journal Asia*, the Japanese Government Pension Investment is the biggest single pension fund in the world, with an asset base of ¥123 trillion or $1.433 trillion. If a mere 1% of the fund's assets were invested into venture capital, this would equal to $14.3 billion, more than seven times the venture capital investment made in Japan in 2008. In other words, rules were made to allow pension funds to invest in venture capital since 1997 but that did not seem to have much impact on the development of venture business in Japan (*Wall Street Journal Asia* 2010).

AnGes was a rising star of Japanese bioventure, being the first successfully listed bioventure, and a showcase of a successful university spinoff from Osaka Univeristy. However, without sustainable funding, it had to spend time and resources to look for the next funding. Funding limitation also caused delays in its drug development process. After the Global Financial Crisis, stock performance and market capitalization began to fall sharply because the biotechnology hype was over and its stock value was kept artificially high prior to the crisis. AnGes was trapped in a vicious cycle as it began to exhaust its funding. Less funding in R&D led to a slower drug development process and fewer clinical development pipelines. Fever pipelines at the later stage of clinical development translated into lower chances of attracting alliances with pharmaceutical companies. This led to delays in targeted milestones, decrease in sales, loss of confidence in its existing investors and new investors. In order to break this vicious cycle, AnGes' hope lies in the promise of its gene therapy and a rebounding economy.

[22] The average out-of-pocket cost per new drug is US$456 million (2000 dollars). US$121 million from early research to preclinical testing and US$355 million from Phase 1 to Phase 3 clinical testing. Capitalizing out-of-pocket costs to the point of marketing approval at a real discount rate of 11% yields a total pre-approval cost estimate of US$802 million.

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