

Current Status of Gene Therapy in Asia

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Asian countries, in particular China, Japan, and Korea, have been aggressively researching and developing gene medicines over the last 15 years or so. In China, an adenovirus expressing p53 was approved for commercial use in the year 2003, and has been on the actual market since then, becoming the world's first commercial gene-based drug. In Japan and Korea, many interesting scientific discoveries have been made, and industrially valuable technologies have been developed. It is particularly noteworthy to see that in these countries, gene therapy has been very keenly nurtured in relation with industrial and financial sectors. Despite remarkable progresses made in Asia, however, their activities have not been visibly noticed by many scientists in the US and European countries. This article briefly reviews key features of the past achievements and recent progresses made in three Asian countries.

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Gene therapy has come a long way since genes were delivered to human subjects for marking and therapeutic purposes by investigators in the National Institutes of Health of the United States in 1989 and 1990, respectively.^{1,2} According to a database administered by Wiley, ~1,200 gene therapy clinical trials have been performed as of July 2007, while the total number of human subjects who have participated in such trials is >12,000.³ Until recently, the field of gene therapy has been dominated largely by investigators in the US and selected European countries. However, in the year 2003, the State Food and Drug Administration of China made a surprising announcement—they officially approved the commercial use of gendicine, a recombinant adenoviral vector expressing p53. Although skepticism and uncertainty have surrounded the use of gendicine, the world's first commercial gene therapy product, the world community has begun to accept it, albeit slowly. Apart from this noteworthy case, Asia as a whole, and in particular the countries of China, Japan, and Korea have been actively researching and developing gene therapy. Together, these countries have already carried out or are performing >40 gene therapy trials, while the combined number of independent research groups in this region is now estimated to be >300. More importantly, the industrial aspects of gene therapy have received a lot of attention in China, Japan, and Korea, resulting in the establishment of a number of start-up companies as well as a positive investment environment within the field of gene therapy at both governmental and private levels. Ironically, this contrasts with the atmosphere found in the West where financial institutions have largely turned their backs on gene therapy, in part due to the slow market entry of gene-based drugs as well as the safety concerns raised from the leukemia case in the X-linked severe combined immunodeficiency trial⁴ and the adenoviral gene therapy death case dating back to 1999.⁵ The goal of this short review is to summarize the current status

of gene therapy in Asia, with a particular emphasis on the projects that have already reached human trial or are very close to doing so. It should be noted that this paper focuses exclusively on China, Japan, and Korea due to the lack of available information on other Asian countries.

CHINA

As mentioned above, China approved the world's first gene therapy product in 2003—the recombinant human p53 adenovirus injection, otherwise known as gendicine. Further unanticipated news came in November 2005 when China's second gene medicine was approved for the market. Scientists in the West could not comprehend the situation, mainly because of the lack of Chinese scientific papers reported in major international academic journals. Contrary to what many in the West believe, China is actually well-versed in the field of gene therapy and is in fact one of the very few countries that approved and performed gene therapy clinical trials during the early 1990s. In 1991, only 1 year after the National Institutes of Health of the United States' adenosine deaminase severe combined immunodeficiency trial, investigators in Shanghai began to transplant collagen matrix-embedded autologous skin fibroblasts engineered to express factor IX using a retroviral vector.^{6,7} Initially, four patients were treated and in two cases, the plasma level of factor IX was reported to have reached 4–5% of the normal level. The same group obtained approval for a clinical trial, again for the hemophilia B case, but this time using adeno-associated virus in the year 1994 and once more in 2003 (<http://www.sfda.gov.cn>).

As summarized in **Table 1**, most gene therapy clinical trials in China target cancer, and a significant number of protocols involve the use of adenoviral vectors, either oncolytic or engineered to express p53, thymidine kinase (TK), interleukin-2, and endostatin among others. Among the many types of adenoviral vectors, the

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Table 1 Gene therapy clinical trials in China, Japan, and Korea

Country	Indication	Gene	Vector	Commencement	Current status	Reference
China	Cancer	<i>p53</i>	Adenovirus	1998	Commercialized	—
	Cancer	Replication-competent adenovirus	Adenovirus	2000	Commercialized	—
	Cancer	Selective oncolytic adenovirus	Adenovirus	2003	Phase II ongoing	^a
	Cancer	TK	Adenovirus	2004	Phase I ongoing	10
	Cancer	IL-2	Adenovirus	2003	Phase I/II ongoing	11
	Ischemic disease	Endostatin	Adenovirus	2004	Phase I ongoing	^a
	Ischemic disease	HGF	Adenovirus	2005	Phase I ongoing	^a
	Cardiovascular disease	VEGF	Adenovirus	2001	Phase I completed	^a
	AIDS	Adeno-vaccine + DNA vaccine	Adenovirus	2004	Phase I ongoing	^a
	Hepatitis B	HBV antigen	DNA vaccine	2005	Phase I ongoing	^a
	Leukemia	Cytokine-activated lymphocyte	Retrovirus (<i>ex vivo</i>)	1997	Phase I completed	^a
	Cancer	Activated dendritic cell	Retrovirus (<i>ex vivo</i>)	2001	Phase I completed	^a
	Late stage gastric cancer	IL-2-modified allogenic gastric cancer cell line vaccine	Retrovirus (<i>ex vivo</i>)	2001	Phase I	11
	Hemophilia	Factor IX	AAV-2	1994	Phase I completed	48
	Hemophilia	Factor IX	AAV-2	2003	Phase I ongoing	^a
	Hemophilia	Factor IX	Retrovirus (<i>ex vivo</i>)	1991	Phase I completed	49
	Glioma	pLTKcSN/VPC (HSV-tk/GCV)	Retrovirus (<i>ex vivo</i>)	1996	Phase I completed	10,50
Japan	Lung cancer (NSCC)	<i>p53</i>	Adenovirus	1998	Phase I/II completed	18
	Esophageal cancer	<i>p53</i>	Adenovirus	2000	Phase I/II completed	19
	Lung cancer (NSCC)	<i>p53</i>	Adenovirus	2000	Phase I/II completed	18
	Lung cancer (NSCC)	<i>p53</i>	Adenovirus	2000	Phase I/II completed	18
	Prostate cancer	HSV-tk	Adenovirus	2000	Phase I/II completed	51
	Lung cancer (NSCC)	<i>p53</i>	Adenovirus	2000	Phase I/II completed	18
	Lung cancer (NSCC)	<i>p53</i>	Adenovirus	2000	Phase I/II completed	18
	Prostate cancer	HSV-tk	Adenovirus	2003	Phase I/II ongoing	—
	ADA deficiency	ADA	Retrovirus (<i>ex vivo</i>)	1995	Phase I/II completed	15
	ADA deficiency	ADA	Retrovirus (<i>ex vivo</i>)	2002	Phase I/II on going	—
	Renal carcinoma	GM-CSF	Retrovirus (<i>ex vivo</i>)	1998	Phase I completed	52
	Mammary cancer	MDR1	Retrovirus (<i>ex vivo</i>)	2000	Phase I/II ongoing	—
	Leukemia	HSV-tk	Retrovirus (<i>ex vivo</i>)	2002	Phase I/II ongoing	—
	Glioma	IFN- β	Liposome	2000	Phase I/II ongoing	21
	Melanoma	IFN- β	Liposome	2003	Phase I/II ongoing	—
	ASO/Burger	HGF	Naked DNA	2001	Phase III ongoing	16
	ASO/Burger	FGF-2	Sendai virus	2006	Phase I/II ongoing	—
Parkinson's disease	Aromatic l-amino acid decarboxylase (AADC)	AAV-2	2007	Phase I/II ongoing	—	
Korea	Melanoma	HLA-B7/ β 2 microglobulin	Liposome	1994	Phase I completed	28
	Melanoma, breast cancer, head-and-neck cancer	Skin fibroblasts transduced with retroviral vectors expressing IL-12	Retrovirus (<i>ex vivo</i>)	1998	Phase I completed	29
	Ischemic limb disease	VEGF165	Naked DNA	2001	Phase II ongoing	30
	Hepatitis B	HBV antigen, IL-12	DNA vaccine	2006	Phase I	31
	Liver cancer	Oncolytic vaccinia virus expressing GM-CSF	Vaccinia virus	2006	Phase I	32
	Chronic granulomatous disease	<i>gp91</i>	Retrovirus (<i>ex vivo</i>)	2007	Phase I/II	—
	Coronary artery disease	HGF	Naked DNA	2006	Phase I started	—
	HIV	HIV antigen, IL-12	DNA vaccine	2006	Phase I	—
	Osteoarthritis	TGF- β	Retrovirus (<i>ex vivo</i>)	2006	Phase I	—
	Prostate cancer	TK, CD	Adenovirus	2005	Phase II	—

Abbreviations: AAV-2, adeno-associated virus-2; ADA, adenosine deaminase; AIDS, acquired immunodeficiency syndrome; ASO, arteriosclerosis obliterance; CD, cytosine deaminase; FGF-2, fibroblast growth factor-2; GCV, ganciclovir; GM-CSF, granulocyte-macrophage colony-stimulating factor; HBV, hepatitis B virus; HGF, hepatocyte growth factor; HIV, human immunodeficiency virus; HLA, human leukocyte antigen; HSV, herpes simplex virus; IFN- β , interferon- β ; IL-2, interleukin-2; MDR1, multi-drug resistance 1; NSCC, non-small cell cancer; TGF- β , transforming growth factor- β ; TK, thymidine kinase; VEGF, vascular endothelial growth factor.

^a <http://www.sfda.gov.cn>.

best known is the recombinant adenoviral vector expressing *p53*, currently being marketed by Shenzhen SiBionio GeneTech. It is based on the first generation adenoviral vector; however, the E1 region is replaced by the human *p53* expression cassette. Gendicine has been administered to >4,000 patients from various ethnic backgrounds with 50 different cancer indications. The accumulated clinical results indicate that gendicine monotherapy is effective,

that it shows a significant synergistic effect when combined with conventional therapies, and that it could significantly improve the patient's quality of life as well as alleviate side effects resulting from ongoing radiotherapy or chemotherapy, especially in the case of late stage cancer patients.⁸ The most commonly observed side effect of gendicine in clinical trials and practice is that of fever at grade I or II, which occurs ~2–4 hours after the injection and

lasts for 2–6 hours, and is self-limiting as it then spontaneously returns to normal.

Replication-competent oncolytic adenovirus is the world's second gene therapy product approved for the market, again by Chinese authorities. According to published data, the phase II trial involved 123 cancer patients and the overall response rate was 78.8% when treatment was done in combination with chemotherapy involving the cisplatin/5-fluorouracil regimen, while the cisplatin/5-fluorouracil treatment alone produced a response rate of only 39.6%. The side effects included fever (45.7%), injection site reactions (28.3%) and flu-like symptoms (9.8%).⁹

The herpes simplex virus TK gene, combined with ganciclovir treatment, was used in two antiangioma clinical trials in the context of retroviral vectors.¹⁰ An adenoviral vector was also used to express TK, in this case to treat patients with non-metastatic liver cancer who were undergoing liver transplantation (web news, data not shown). It was claimed that no relapse and/or metastasis were found during the 1-year follow-up period. In another trial, the human gastric cancer cell line MKN45 was engineered to express interleukin-2 by a retroviral vector, inactivated by irradiation, and cryopreserved before carrying out subcutaneous injection to 16 patients suffering from late stage gastric cancer. It was reported that some of these patients showed improvements in selected immune parameters.¹¹

A variety of gene therapy research endeavors are currently under way in China and many of them focus on cancer gene therapy. The genes used in various studies include *TK*, *p16*, *p21*, granulocyte-macrophage colony stimulating factor, *B7-1* and many others. It is interesting to note that unlike in the West, hepatoma is a preferred target disease as liver cancer is highly prevalent in China. Encouraging progress has been made in the field of anti-angiogenic cancer immunogene therapy, based on xenogenic endothelial cells or the *Xenopus* vascular endothelial growth factor gene.^{12,13}

Chinese scientists are very active in the field of gene therapy. The West does not have a good grasp of China's activities and seriousness mainly because of the fact that most scientific data are published only in Chinese journals. This is indeed one of the major obstructions that Chinese scientists will eventually have to deal with in order to enter into the world arena.

China is very advanced in the commercialization of gene therapy products as demonstrated in the case of gene therapy and oncolytic adenovirus H101. Shenzhen SiBiono GeneTech. was the first gene therapy company in China. It has established a production process and a quality control system needed for the manufacturing of gene therapy. It is a leader in the gene therapy field since it was involved in drafting the "Points to Consider for Human Gene Therapy and Product Quality Control" guidelines set by the Chinese regulatory authority, State Food and Drug Administration of China, in March 2003. The company even helped to translate this Chinese document into English. As a result of this success, many are following SiBiono's example. In this regard, it is quite interesting to see that many gene therapy companies in China are using adenoviral vectors as their platforms.

Another base for the gene therapy industry within China can be found in the Shanghai region. Shanghai Sunway BioTech. is a gene therapy company involved in commercializing the world's

second commercial gene medicine, oncolytic adenovirus H101, from the year 2006. Shanghai Fudan-Yueda BioTech focuses on the development of drugs against a variety of infectious diseases. One of their gene therapy targets is hepatitis B virus. Chengdu Hoist Group and Double Bioproducts in Guangzhou specialize in the development of adenoviral vectors as anticancer agents.

Despite the significant progress made in China, with reference to commercial application of this technology, there are two areas in which China needs to make improvements. First is the issue of intellectual property. Until quite recently, a significant number of patents covering original gene therapy discoveries and inventions made by scientists in the West were not filed in China, and thus were freely available for commercial development there. Indeed, many gene therapy products under development in China originated from the West. However, as China is now part of the World Trade Organization, there is an expectation for it to be in compliance with World Trade Organization rules and regulations. Another issue is the gene therapy regulatory procedure in China. This has been modernized, in some ways coinciding with the commercialization of gene therapy, as summarized in a recently published paper.¹⁴ It is now in better alignment with international standards and will continue to develop progressively.

JAPAN

Japan is the world's second most advanced country according to many criteria, including its economy, science and technology, and its biotech market. Despite this high position, Japan has maintained a relatively low profile in the field of gene therapy, due largely to the conservative stance taken by the Japanese regulatory agency and also due to the hesitation of established pharmaceutical companies in becoming involved with this new technology. However, since 2002, the environment has changed significantly with the active performance and financial success of several biotech companies.

Japan's first gene therapy trial was approved in 1995 by the Ministry of Health and Welfare for a severe combined immunodeficiency patient with adenosine deaminase deficiency. The investigators in Hokkaido University treated one patient with retroviral vectors imported from Genetic Therapy (Gaithersburg, MD), using the same protocol employed by the Anderson group. After gene therapy, the patient was able to attend school and enjoy a relatively normal life.¹⁵ However, it should be noted that the patient was treated in parallel with protein replacement therapy. Since this first trial, 19 clinical protocols have been approved; 14 for cancer, 2 for adenosine deaminase severe combined immunodeficiency, 2 for vascular diseases and a remaining one for Parkinson's disease, as summarized in [Table 1](#).

One of the most advanced gene therapy programs is of therapeutic angiogenesis developed by the Osaka Group. From the year 2002, 22 patients with arteriosclerosis obliterance or Buerger disease have been treated, using naked plasmid DNA designed to express hepatocyte growth factor (HGF). The primary endpoints were not only the safety but also the improvement in ischemic symptoms at specified time points after DNA injection. The reduction of ulcer size was seen in 7 out of 11 ulcers after gene therapy.¹⁶ Intramuscular injection of naked HGF plasmid was safe and generated a satisfactory improvement of blood

pressure in ischemic limbs with >70% efficiency. Encouraged by these results, a phase III clinical trial was initiated in Japan with sponsorship from the biotech company, Anges MG. This trial was finished in June, 2007, and Anges MG will make an application for the HGF gene drug to the Ministry of Health, Labor and Welfare in Japan.

Most of the gene delivery vehicles used in Japanese clinical trials are adenoviral and retroviral vectors that have been developed and manufactured mostly by US groups. The first cancer gene therapy trial involved the use of the cancer cell vaccine engineered with a retroviral vector expressing the granulocyte-macrophage colony-stimulating factor gene and was carried out by investigators at the University of Tokyo and Tsukuba University.¹⁷ The p53 gene-loaded adenovirus vector, ADVEXIN, developed by Introgen Therapeutics (Houston, Texas), has been extensively tested as an anticancer agent in the multi-center trial for lung cancer mainly in Okayama University and for esophageal cancer in Chiba University. Fifteen lung cancer patients received 10⁹–10¹¹ adenovirus vectors multiple times. Thirteen out of fifteen patients were evaluated. One showed a partial response, 10 had stable disease, and two had progressive disease.¹⁸ One patient survived for >3 years. Out of 10 esophageal cancer patients who received this gene therapy, most of the patients experienced stable disease.¹⁹

The researchers at Jichi Medical School are planning to treat Parkinson's disease patients with adeno-associated virus 2 expressing aromatic-L-amino acid decarboxylase. This trial is being led by Ozawa.²⁰ The clinical grade vector will be provided by Genzyme (Cambridge, MA).

Sendai virus is uniquely Japanese in that it was originally discovered in Japan. The Investigators at DNAvec developed Sendai virus as a gene delivery vehicle. It is different from other viral vectors in that it is based on the RNA virus, which does not use DNA in its life cycle unlike the retrovirus. DNAvec obtained approval from the Japanese regulatory agency to conduct a clinical trial for arteriosclerosis obliterance patients using the fibroblast growth factor-2 gene. Clinically applicable cationic multilamellar liposomes were developed by Yoshida at Nagoya University.²¹ Plasmid DNA containing the β -interferon gene, mixed with this liposome has been used to treat glioblastoma at Nagoya University and melanoma at Shinshu University. Various types of nanomicelles, previously proven to be useful for the delivery of anticancer drugs, are being investigated for their possible use as gene delivery tools.²²

Although established pharmaceutical companies in Japan are hesitating to get involved in gene therapy, small start-up biotech companies, collectively called venture companies, are very actively pursuing gene therapy technology for commercial purposes. It is interesting to note that most of these start-up companies are based on the discoveries and inventions that originated from academic institutions. Anges MG is one of the first gene therapy companies in Japan to go public and be listed on the stock market. Armed with the capital it has raised, Anges MG is actively pursuing clinical trials for its HGF-based gene medicine in the US as well as in Japan. The hemagglutinating virus of Japan envelope vector was found to convert live Sendai virus to non-viral cargo by Y.K. at Osaka University.²³ The clinical grade hemagglutinating virus of

Japan envelope vector is being produced by GenomIdea with an aim at applying the vector to cancer and infectious disease. The oncolytic adenovirus driven by the human telomerase promoter was developed by a group at Okayama University²⁴ and in-licensed by Oncolys BioPharma. A fragment of HGF called NK4 was found to contain strong antiangiogenic activity, and Klingle Pharma, is planning to initiate a cancer gene therapy trial using an adenoviral vector loaded with NK4. Based on the Williams group discovery in the US,²⁵ the investigators at Takara Bio commercialized a fragment of fibronectin, now brand named as Retronectin, that could highly increase retrovirus-mediated gene delivery efficiency.^{26,27} This company is currently setting up production for the clinical grade plasmid.

The chief difficulty facing Japanese scientists involved in gene therapy is the extensive procedural process imposed on them by the regulatory agency. Although simplified and improved from time to time, these procedures still take up a lot of time and effort. There are very few professional clinical coordinators in the field of gene therapy in Japan. More educated and trained coordinators are absolutely needed to further develop and promote human gene therapy.

Despite these difficulties, Japan has a bright future in the field of gene therapy. It has the world's second largest drug market as well as capital investors that are willing to invest in gene therapy for the long term. It also has highly qualified medical facilities as well as a legal infrastructure that meets world standards, including those regarding intellectual property rights. The gene therapy community is also excited by the intense interest in start-up biotech companies shown by the financial sector. The Japan Society of Gene Therapy was organized in 1994 and currently has >700 active members. The Japan Society of Gene Therapy is determined to promote gene therapy by educating young scientists, supporting medical doctors, and serving as the main communication channel with governmental agencies.

KOREA

Korea is proportionately small in terms of its population and market relative to its two giant neighbors, China and Japan. Thus far, five gene therapy clinical trials have been or are being conducted in Korea; two before the establishment of the formal gene therapy guideline in 1998 and another three thereafter (**Table 1**). The first clinical trial, performed with approval from the institutional review board in the year 1994, used liposome-treated plasmid DNA containing an allogenic major histocompatibility complex class I (human leukocyte antigen-B7/ β 2-microglobulin) gene for nine patients; four with melanoma, two with head-and-neck cancer, two with lung cancer, and one with stomach cancer. All patients were refractory to conventional treatments.²⁸ Park's group conducted the second trial in 1998 using skin fibroblasts transduced with a retroviral vector expressing interleukin-12 for patients with advanced malignancies of various histological types with tumor lesions accessible from the body surface, which included melanoma, breast and head-and-neck cancers.²⁹ A clinical grade retroviral vector was imported from Lotze's group in the US with approval from Korea's Ministry of Health and Social Welfare. This trial can be regarded as Korea's first clinical trial that used a protocol and materials of globally

recognized standards. Despite these two trials, during its early stages in Korea, the progress of gene therapy was significantly held back largely because of the slow establishment of regulatory procedures related to gene therapy.

Early confusion surrounding the regulatory procedures gradually subsided and a gene therapy guideline was finally set up by the Korean Food and Drug Administration in 1998. The guideline is very similar to that of the European Medicines Agency and the US Food and Drug Administration, except for minor differences. The first clinical trial performed after the formal establishment of the new guideline was gene therapy for ischemic limb disease using naked DNA expressing VEGF165. The phase I trial produced encouraging therapeutic effects, showing an improvement in ankle brachial index, claudication, ulcers, among others.³⁰ Phase IIA trial was completed in 2006 and the data are currently being analyzed. The second trial involves the injection of naked DNA expressing selective human immunodeficiency virus antigens to infected individuals receiving highly active antiretroviral therapy treatment. Another trial uses DNA vaccine comprising hepatitis B virus genes plus genetically engineered interleukin-12 DNA (IL-12N222L) in chronic hepatitis B patients being treated with lamivudine.³¹

Finally, there is a unique gene therapy procedure employing the oncolytic vaccinia virus with a defect in the TK gene, incapable of viral replication in normal cells but engineered to express granulocyte-macrophage colony-stimulating factor in an attempt to activate the patient's immune system. The data from the animal experiments were highly encouraging³² and phase I trial is under way.

Three separate clinical trials sponsored by two companies have recently been approved by the Korean Food and Drug Administration. First is the phase I trial for osteoarthritis supported by Kolon. This trial is using a retroviral vector expressing transforming growth factor- β , but it is different from all other *ex vivo* approaches performed so far in that the engineered cells are irradiated and designed to be applied to all patients.^{33,34} This clinical protocol has also been approved by the US Food and Drug Administration.

The two other approved protocols are from ViroMed. One is the phase I/II gene therapy trial for chronic granulomatous disease involving an *ex vivo* approach in which the normal gp91 gene is delivered to hematopoietic CD34⁺ cells with a retroviral vector. The retroviral vector used in this trial is the first of its kind in that it does not contain any viral coding sequences unlike its predecessors—LN series vectors or MFG.^{35–37} It is claimed to be safer than other vectors in terms of replication-competent retrovirus production because the possibility of homologous recombination is theoretically nil between the coding sequences in the vector and the packaging genome or the endogenous retrovirus. In February 2007, an 18-year-old male patient was treated with autologous CD34⁺ cells engineered to contain the normal gp91 gene. The other trial is for gene therapy for coronary artery disease involving naked DNA containing the genetically modified HGF gene designed to simultaneously express high levels of two isoforms of this angiogenic protein. As of April 2007, two patients have received this naked DNA injection directly to the affected heart region during open heart surgery. The same

product is also being used in a phase I trial of ischemic limb disease led by investigators in the US. A high efficiency expression plasmid system called pCK, which is to be used in this trial, is unique in that it produces a high level of gene expression *in vivo* and the actual protein is detectable by enzyme-linked immunosorbent assay or Western blot, a rare event in the field of naked DNA gene therapy.³⁸

Korea's first government-funded gene therapy research began in 1994. Since then, the field has been growing steadfastly and there are now ~50 independent research groups that claim to work on gene therapy. Korean investigators have actively been reporting the results of their gene therapy research. Kim's group reported the development of a new type of oncolytic adenovirus and is planning to consider an Investigational New Drug application in Korea with a primary target being liver cancer. Lee *et al.* found that the expression of the thymosine β 10 protein could produce potent antitumor activities in ovarian cancer cells in the context of adenovirus gene therapy³⁹ and held a pre-Investigational New Drug meeting with the Korean Food and Drug Administration for the possibility of a gene therapy trial. Adeno-associated virus is being actively developed for Parkinson's disease.⁴⁰ There are also investigators actively pursuing RNA-based gene therapy, for example, using ribozymes,⁴¹ small interfering RNAs,⁴² and aptamers.⁴³ New delivery and expression systems have always been of major interest, for example, tumor cell-specific expression,⁴⁴ new polymers,⁴⁵ and an improved version of feline immunodeficiency virus system⁴⁶ among others.

While most of Korea's well established pharmaceutical companies are still hesitant about getting involved in gene therapy, relatively small sized venture companies are aggressively pursuing business-oriented gene therapy research and development. Based on the records of performing human trials, two companies stand out: Dong-A Pharmaceuticals, which has two ongoing gene therapy trials (ischemic limb disease and acquired immunodeficiency syndrome) in collaboration with two venture companies; and ViroMed, which focuses on cell and gene therapy products and is listed on Korean Securities Dealers Automated Quotations (equivalent to National Association of Securities Dealers Automated Quotations system in the US). ViroMed originated from Korea's first government-funded academic gene therapy research group at Seoul National University. Though small, it aggressively pursues the research and development of gene therapy products, carrying out 4 separate clinical trials in the US, China as well as in Korea. There are at least three other companies running gene therapy programs, but actual clinical trials appear to be at least 2–3 years away from the time of this report.

With backing from associated international alliances, the Korean Society of Gene Therapy was established on 1 December 2006. Korean Society of Gene Therapy will begin official engagement with ~100 members. The major goals of Korean Society of Gene Therapy are to scientifically, educationally, and industrially promote gene therapy as well as to represent Korean investigators during interaction with other international gene therapy societies. Korean Society of Gene Therapy also anticipates becoming a positive communication channel between investigators and the Korean regulatory agency.

CONCLUSION

During the early exploratory stages of gene therapy, Asian countries were slower than their Western counterparts. During the early 1990s, scientists in this region were busy duplicating what US investigators had previously done, and industry was largely ignorant of this newly emerging technology. However, from around the year 2000, China, Japan, and Korea have emerged as strong contenders in the field of gene therapy, while the West has remained preoccupied with the death case and later the leukemia incidence. Though these cases deserved serious investigation, industrial and financial communities in the West seem to have become ensnared in the safety issues resulting from the adenoviral death incidence and the retroviral insertional mutagenesis case. Ironically, the dampening atmosphere in the West provided Asian countries with the opportunity to catch up. Encouraged by the announcement of the completion of the human genome project and fueled by the successes of the information technology industry, these countries have been eager to explore the field of biotech and gene therapy has been one of their favorite target areas.

Since the year 2000, investigators in this region have begun to produce new and innovative data that has industrially meaningful implications. In Japan for example, Sendai Virus was developed as a gene delivery vehicle, which has made the patriotic Japanese feel proud of themselves, as the Sendai virus was initially discovered in Japan.⁴⁷ Additionally, a Japanese company was able to commercialize a fibronectin fragment that significantly increases retroviral transduction efficiency, which is now being used in almost all retroviral gene therapy clinical trials. Meanwhile in Korea, a high efficiency naked DNA was invented that ensures a therapeutically meaningful level expression of therapeutic protein *in vivo*;³⁸ also murine leukemia virus-based retroviral vectors have been improved for their efficiency and safety,^{35–37} thus reviving interest in this seemingly out-dated gene delivery vector. Lastly, in China, which lays claim to having developed the world's first and second gene-based medicines, gene therapy has been aggressively promoted at both governmental and industrial levels.

Of course, there are several areas that these Asian countries have to improve in. Nonetheless, these countries are armed with financial sectors willing to take risks, strong supports from the government, qualified regulatory agencies, and hard working innovative investigators. The scientists in these countries now plan to establish the (tentatively named) "Asian Society of Gene Therapy" and aim to hold its first symposium in 2007 in Japan. Through this Society, it should be possible to find ways to complement weaknesses and synergize strengths. It would be no exaggeration to say that within the next few years, Asia has the potential to become an epicenter in the industrial and financial aspects of gene therapy.

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