

China's Gene Therapy Drug

BY SHELDON KRIMSKY

Do Shenzhen SiBiono Gen-Tech's Claims Hold Up?

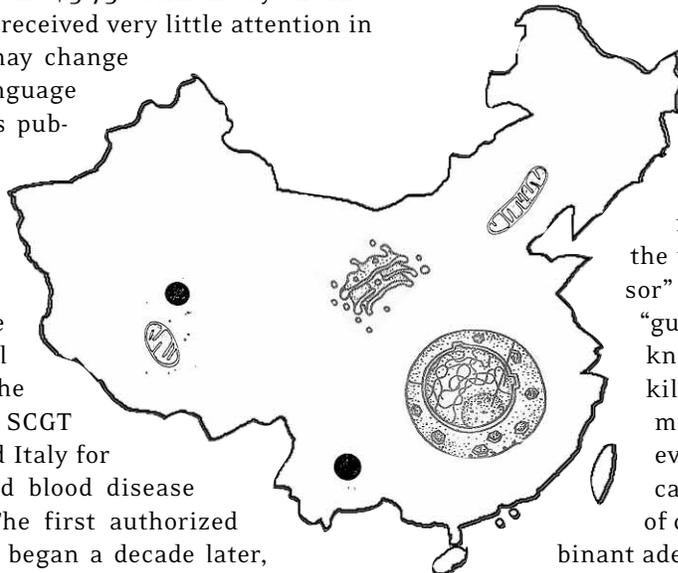
The first paragraph of the May-June 2005 *China Business Review* reads, "China has slipped into an influential role within the global biotech industry."¹ Indeed, the event that justifies this attribution is China's development and commercialization of the world's first gene therapy drug. The drug, called Gendicine, was first approved for clinical use in gene therapy by the State Food and Drug Administration (SFDA) of China to treat head and neck squamous cell carcinoma (HNSC) in January 2004.² Of the 2.5 million people in China diagnosed with cancer each year, it is estimated that 10 percent or about 250,000 have squamous cell cancer.³ According to the *World Gene Therapy Market Research Report*, revenues from gene therapy products could reach \$5.73 billion by 2011.⁴ Nevertheless, the drug has received very little attention in Western societies. This may change with the first English language report of the clinical trials published this month in the journal *Human Gene Therapy*.

Somatic Cell Gene Therapy (SCGT) was one of the earliest goals of the nascent pharmaceutical biotechnology industry. The first clinical trials using SCGT began in 1980 in Israel and Italy for patients with the inherited blood disease beta thalassemia major. The first authorized trials in the United States began a decade later, after guidelines had been developed and protocols had undergone extensive review by scientists and bioethicists. Over this 15-year period, there have been more than a thousand approved clinical trials worldwide. However, despite a significant research and development investment in SCGT, efforts at developing a successful therapy have met with countless failures and episodic controversy.⁵

Surprisingly, the announcement by Chinese scientists of the first SCGT drug was largely ignored by the major media outlets in the United States. A number of science journals and biotechnology electronic bulletin boards ran it as a news story. *Human Gene Therapy* published an editorial on the announcement, along with a paper by Zhaohui Peng, the Chinese scientist who played a major role in developing and testing the drug.^{6,7} If this drug is as successful as the Chinese researchers claim, then its approval for clinical use is a significant medical achievement. Why, then, has the Euro-American response been so subdued? The answer

may lie in how the drug was tested and what the test data show. In addition, it may lie in the fact that both American and French researchers have overstated the progress in human gene therapy. To answer this question, we must examine the clinical data the Chinese scientists have gathered and claims they have made in support of their human gene therapy drug, while raising further questions about the robustness of their clinical trials. The commercial interests in the drug by its leading scientific spokesperson must be discussed, as well.

WHAT IS GENDICINE?



Gendicine is a recombinant adenovirus with some genetic pieces removed and others added. Adenoviruses are a class of viruses that elicit respiratory, intestinal and eye infections in humans. One of the main added components of Gendicine is the p53 gene – a so-called “tumor suppressor” gene, or what others have termed the “guardian of the genome” because it is known to express an oncoprotein that kills tumor cells. For years, p53 and its mutations have been studied for their relevance to the cause and prevention of cancer. Similarly, there have been dozens of clinical trials using variants of a recombinant adenovirus for human gene therapy. Thus,

Gendicine's composition makes it a true hybrid of the biotech age. In addition to the original adenovirus and the p53 components, Gendicine also contains gene segments from a Rous Sarcoma Virus and Bovine Growth Hormone. According to the drug's inventor, “after Gendicine administration, the adenoviral particle infects tumor target cells and delivers the adenovirus genome carrying the therapeutic p53 gene to the cytoplasm and the cell nucleus for transcription and translation of the p53 gene. The expressed p53 gene appears to exert its antitumor activities...”⁸ The Chinese developers of Gendicine do not know for sure how it works. They have posited theories from studies in the existing theories. Yet they are convinced about its safety and efficacy, based only on the tumor suppression qualities of p53. The researchers also believe that their drug works synergistically with radiation treatment or chemotherapy. They found that patients with low levels of p53 expression

are more resistant to radiation and chemotherapy, compared to patients with higher levels of p53 expression. A case report of Gendicine's success for the treatment of advanced liver cancer was reported this month in the *British Journal of Gastroenterology*.⁹

DR. ZHAOHUI PENG

Dr. Zhaohui Peng was trained in gene therapy techniques in Japan and the United States before he began his research in China, where he started a company called Shenzhen Sibiono Gen-Tech. He also published China's first book on gene therapy in 1994. Dr. Peng obtained a drug license from the State Food and Drug Administration of China to manufacture and administer Gendicine in clinical trials. According to Peng, the total investment in Gendicine was about 9.66 million U.S. dollars, one fourth of which came from various Chinese government sources including the Ministry of Science and Technology, a state high tech fund, and the Shenzhen municipal government.



After five years of clinical trials, Dr. Peng claims the only side effects observed for Gendicine have been a self-limiting fever. However, it was approved for commercial use after it was administered to about 130 patients in clinical trials, a much smaller number of human test subjects than is usually accepted by the USFDA for commercial drug approval. This, in combination with Dr. Peng's significant commercial investment in Gendicine, is a compelling reason to further scrutinize the clinical trial data.

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CLINICAL DATA

Dr. Peng published his clinical trial data for head and neck squamous cell carcinoma in *Human Gene Therapy*. In phase I trials, where safety is tested, 12 patients with advanced laryngeal cancer were divided into three groups and given escalating doses of ten intratumoral injections of Gendicine before and after surgery. By administering the drug before and after surgery, the investigators are exploring various hypotheses about the drug's effectiveness including apoptosis (cell death) of tumor cells, activation of immune response that would prevent the development of tumor cells, and inhibition of DNA repair of tumor cells targeted by chemicals and radiation. The investigators measured fever, wound healing after surgery, and relapse. They observed a "self-limiting" fever in one patient, but found no association

between the use of Gendicine and slower wound healing after surgery, and observed no patient relapse for a five year period after treatment, whereas the relapse rate for patients with advanced laryngeal cancer after surgery is generally about 30 percent. Dr. Peng wrote, "So far, no severe side effects have been found in more than 2,500 patients treated with Gendicine."¹⁰ While Dr. Peng claims to have observed several thousand patients, the published clinical trial data describes treatment to only about five percent of that number. Also, relapse is not a precise medical measure, and this study does not make clear what the parameters for defining a relapse are. We are also not told whether this was a double-blind study.

The phase II and III clinical trials in this study involved measurements of efficacy covering a 12 week period of treatment. Dr. Peng writes, "A multicenter, concurrently controlled randomized clinical trials was conducted in which Gendicine was administered to 135 patients with head and neck squamous cell carcinoma. ...The patients were divided randomly into two groups: one group received gene therapy in combination with radiotherapy (GTRT) and the other group received radiotherapy alone (RT)." This is clearly contradictory (135 patients are divided up between the experimental group and the control group) but that may be the result of a language or editing problem.

From the tables presented, it appears that there were 135 subjects, 85 percent had nasopharyngeal cancer and 77 percent of them were in their late stages (III or IV) and had failed either radio- or chemotherapy or were not eligible for surgery. Of the 135 subjects, 63 received Gendicine.

Group	Complete Regression	Partial Regression	Stable Disease	Progressive Disease
Gene Therapy and Radiotherapy 63 original, 56 after 12 weeks	36 (64%)	16 (29%)	4 (7%)	0 (0%)
Radiotherapy alone 72 original, 63 after 12 weeks	12 (19%)	38 (60%)	13 (21%)	0 (0%)

Data on a Gendicine Clinical Trial in China

The outcome measure of complete tumor regression (as measured by computed tomography or magnetic resonance imaging) was three times greater when the treatment included radiation and Gendicine compared to just radiation therapy. However, partial tumor regression was largely more successful with just radiation therapy. We are told that most of the subjects had failed to respond to radiation or chemotherapy. Somehow, when radiation therapy is combined with the recombinant adenovirus with the p53 gene, it yields complete regression in 64 percent of those treated. The synergism that Dr. Peng's research team believes is occurring between these treatments is unexplained.

Dr. Peng also describes another clinical trial of Gendicine for patients who have advanced liver cancer. A total of 150 patients were divided up into two groups: 68 were treated with Gendicine and chemotherapy and 82 patients were treated by chemotherapy alone. According to Peng, “the preliminary results showed that Gendicine in combination with TACE [chemotherapy] is effective for the treatment of HCC [Hepatic Cell Carcinoma] to enhance patient survival rate and to improve quality of life.”¹² In fact, none of the 150 patients had a complete response to either treatment protocol, while 45 of those treated with Gendicine and chemotherapy versus 42 of those treated exclusively with chemotherapy had a partial response. The survival data for HCC patients was the most provocative. Of the 68 patients given chemotherapy and Gendicine, 52 (77%) survived after 6 months compared to 19 out of 82 patients (23%) just on the chemotherapy.

Of course it would be important to know whether the experimental and control subjects were totally unaware of who was getting the Gendicine because the knowledge that one is receiving an experimental drug might in itself give people hope and extend life. There is a rich literature on the placebo effect in medicine. Because we have no evidence in this published study whether patients knew they were receiving the drug, we must leave open the possibility that their survival could be due to a placebo effect. It is also important to know what happened to the people who dropped out of the clinical trial before the final weeks of treatment.

IMPLICATIONS

Chinese drug authorities routinely do not approve a new drug if it has not been approved in the United States. Gendicine has been an exception—evidence of the maturation of the Chinese biotech industry and the persuasiveness and celebrity of Dr. Peng. Sandro Rusconi, a Swiss scientist, summed up the status of Gendicine as follows:

The use of recombinant adenoviruses carrying a “healthy” version of the tumor suppressor gene p53 for the treatment of human cancers has been widely investigated.

Clinical trials with this kind of approach have reached phase II and are just entering phase III, at least according to available registries (example: Wiley database). The official documentation about the results obtained in phase I and phase II is partly encouraging and partly disappointing.

Given the controversial results, it is very surprising to hear that a product based on this principle has been allegedly approved for commercialization in China.

More surprisingly the available news talk about the largest clinical trial having involved 120 patients. This number is suspiciously small for the traditional criteria of a rigorous phase III trial.

At this very moment, many western specialists are rather surprised by this move. It remains to be estab-

lished whether this prospected drug fulfils the standards of efficacy and safety that are usually required by good clinical practice. My preliminary feeling is that at the basis of this claim there are more financial interests than genuine medical-scientific progresses.¹³

In his supportive but cautious review of the first English language publication of the Gendicine trials, James M. Wilson, editor of *Human Gene Therapy*, indicated that the paper by itself had insufficient information to allow an independent assessment of the SFDA's decision to approve the drug for commercial sales. There is no indication that Gendicine has been submitted to the USFDA for review.

Public awareness about Gendicine is growing. One Canadian pharmacy website, www.drugdelivery.ca, is telling consumers: “Doctors are now extending the treatment, named Gendicine, to patients with lung and stomach cancer. Injected directly into the tumour, Gendicine works by, in effect, programming cancer cells to commit suicide. About 400 patients so far have been treated with the drug in eight-week courses which cost the equivalent of 1,800 pounds.”

The history of gene therapy research should teach us to proceed with extreme caution. Many of the dangers of injecting viruses into patients were initially understated and suppressed. After the death of Jesse Gelsinger, a government hotline set up for victims of gene therapy experiments revealed 652 cases of adverse events, most of which went unreported, and included six unexplained deaths. Except for the published article in *Human Gene Therapy*, there is virtually no scientific or medical information about this drug in the world scientific community. We also know that there is significant private investment in the drug among its developers. These factors should make us extremely wary of the claims coming from Dr. Peng and his company, Shenzhen Sibiono Gen-Tech. Moreover, from a human rights perspective, an international medical group should do an independent evaluation of Gendicine at least to be assured that it is not more dangerous than the diseases it is promoted for. ■■■

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About the Artist



The image on the cover of this issue of *GeneWatch* is by Yvonne Blanco. A graduate of the Rhode Island School of Design, Blanco currently works as a Graphics Engineer. Her paintings and typography work has been exhibited in various countries and she enjoys building and riding chopper bicycles with the Subversive Chopper Urban Legion (SCUL).

Cloning in America

BY KELLI WHITLOCK BURTON

The Genetics and Public Policy Center Surveys the Nation

The Genetics and Public Policy Center, a part of the Phoebe R. Berman Bioethics Institute at Johns Hopkins University, compiled the survey information found in the following article for a 2005 publication entitled "Cloning: A Public Policy Report." This article is a summation of the Genetics and Public Policy Center's findings on the public opinion of cloning, stem cell research, and the legal environment which regulates these fields. The original report can be found in its entirety at www.dnapolicy.org. The author of this article is a freelance writer who compiled the report on behalf of The Genetics and Public Policy Center.

The term cloning evokes strong responses among Americans. Opposition to cloning arises from several concerns, including ones regarding the destruction of human embryos, usurping Divine authority, interfering with the natural order, exploitation of the women from whom human eggs are obtained, and the impact of cloning human beings on those who are cloned. Support for cloning originates pri-

marily from its potential to yield fundamental new research insights and to lead to new therapies to treat devastating illnesses.

THE STATE OF CLONING RESEARCH

Although there have been no documented cases of human reproductive cloning, scientists have been attempting to clone animals through somatic cell nuclear transfer (SCNT) for several decades. In 1996, Dr. Ian Wilmut at the Roslin Institute in Scotland and colleagues used a nucleus extracted from a mammary cell of a six-year-old sheep to create Dolly, born on July 5, 1996.¹ Dolly was the first animal cloned from a nucleus obtained from the cell of an adult animal. Since then, scientists have used SCNT to clone a variety of mammals, including mice, rabbits, pigs, cats, cows and a mule.²⁻¹⁰ In December 2004, the company Genetic Savings & Clone announced the sale of the first cloned pet to a woman in Texas whose previous cat had died.¹¹

Notwithstanding these research and commercial mammalian cloning examples, SCNT to date has been a very inefficient process, in that most embryos created via SCNT do