

# The Cancer Crisis

Cancer is one of the greatest health challenges facing the world today with over 10 million new cases of cancer every year. According to The American Cancer Society, 1,444,920 new cancer cases were reported for 2007; 766,860 among men and 678,060 among women in the USA alone. In China, the world's most populous country, cancer is the number one cause of death and disease.

### New Weapons Against Cancer

The global fight against cancer continues with traditional treatments like chemotherapy and radiotherapy. However, emerging gene therapy treatments have shown great promise. Novel approaches like AMDL Inc.'s Combined Immunogene Therapy (CIT) seek to stimulate the body's T-cells to directly attack cancer cells without the adverse side effects of chemotherapy and radiotherapy. Introgen Inc. is currently in US phase III trials with its gene therapy drug Advexin which treats cancers of the head and neck. One of the most exciting developments to date is China-based Benda Pharmaceutical's Gendicine, the world's first commercialized gene therapy medicine for the treatment of cancer. Gendicine is China SFDA approved (Jan. 2004) and is currently being administered to patients in China. The drug uses a shuttling system based on the adenovirus which normally causes the common cold. However, the adenovirus has been dramatically altered to carry the p53 gene, which is a gene that limits cancer growth, into the tumor cell to kill it. Gendicine is generically known as Recombinant Human Ad-p53 (rAD-p53). More than 5,000 Chinese patients have already been treated and over 400 foreigners from over 30 countries including the U.S., Canada, England, and Australia have also been treated with Gendicine in China according Benda Pharmaceutical.



Figure 1 Gendicine uses the adenovirus to deliver p53 gene

## Explosive Growth for Gene Therapy:

Benda estimates Gendicine sales of \$6.2 million for 2007 and they expect sales of \$16 million for 2008. According to ClinicalDiscovery.com and a recent Frost & Sullivan report, the world gene therapy market is likely to experience explosive growth at a compound annual growth rate (CAGR) of 68.30 per cent over the period 2004 to 2011 despite challenges including a lengthy approval process. As more products reach the market, revenues from gene therapy are projected to reach USD 5.73 billion by 2011. Furthermore, Benda Pharmaceutical states that in China alone the anti-cancer drug market surpassed \$2.6 billion in 2005. The company also reports that the demonstrated efficacy of its Gendicine gene therapy has translated into immediate financial returns claiming \$3.8 million in orders in one day following a recent biotech conference in China.

### Gene Therapy Drug Reaches US Phase III Clinical Trials

US-based Introgen Inc. is now working closely with the US FDA to perform Phase III level clinical trials of Advexin, its promising gene therapy drug. Introgen is in the FDA designated Fast Track Drug Product Development program seeking Advexin approval for the treatment of head and neck cancers. Advexin gene therapy combines the p53 tumor suppressor with a non-replicating, non-integrating adenoviral delivery system. Similar to the Gendicine approach, Advexin employs an adenovirus and p53 gene strategy. The p53 gene is one of the most potent members of a group of naturallyoccurring tumor suppressors, which act to kill cancer cells, arrest cancer cell growth and protect cells from becoming cancerous. Introgen's clinical trial strategy for Advexin is to test it in a variety of life-threatening cancers for which there are no effective treatments.



### A Gene Therapy Success

Studies carried out by Introgen using Advexin gene therapy (under an accepted FDA protocol) have shown that the treatment is effective against Li-Fraumeni Syndrome (LFS), a genetic disorder that greatly increases the risk of developing several types of cancer, particularly at a young age. The majority of LFS families have mutations in the p53 tumor suppressor. Advexin p53 therapy has been successfully used on a Compassionate Use basis under a protocol accepted by the FDA. Based upon its initial findings, Introgen has decided to continue to make Advexin gene therapy available on a Compassionate Use basis to qualified LFS patients through physician-sponsored protocols at qualifying institutions.

# Treating Cancer in US Approaching \$80 Billion Cost Annually

Cancer is a leading cause of death in the United States, where approximately 1.4 million people are newly diagnosed with cancer and approximately 560,000 people die from the disease each year. According to Introgen and National Institutes of Health (NIH) estimates, the annual direct cost of treating cancer patients in the United States is approximately \$78.2 billion.

## AMDL Inc. Pursues Innovative Gene Therapy Approach

US and China-based AMDL Inc. owns and continues to develop US patented Combination Immunogene Therapy (CIT) technology with intent to produce a vaccine for the treatment of various cancers. The technology was developed by Lung-Ji Chang, Ph.D. at the University of Alberta, Edmonton, Canada, and acquired by AMDL in September 2001. The company then applied for and received a US Patent for CIT in May 2004. According to AMDL, most gene therapy to date has attempted to replace all defective genes in every cancer cell, which is theoretically and practically impossible. AMDL's new approach combines the granulocytemacrophage colony-stimulating factor (GM-CSF) gene with the B7-2 gene to enhance the antitumor immune response. CIT targets cancer cells for immunological attack, while simultaneously stimulating a stronger immune response.

# CIT Gene Therapy Builds Immune System and Destroys Cancer Cells

The CIT technology works by simultaneously incorporating two genes directly into the patient's tumors to enhance their immune system's natural ability to destroy cancer cells. The GM-CSF gene increases the numbers of T-cells which can engulf and kill tumor cells. After the B7-2 gene is integrated into the tumor cells, the B7-2 protein sits on the surface of the tumor cells to help T-cells locate and destroy the tumor cells. The B7-2 protein is a molecular flag as well as a co-stimulatory molecule for T-cells. As the T-cells prevail over the cancer cells, the tumor is destroyed. For those patients known to be at risk because of a family history for certain types of cancer, CIT





could eventually be used to build or protect the patient from acquiring cancer by preparing the patient's immune system to destroy that specific kind of cancer cell.

## CIT Benefits and Innovations

AMDL reports that with CIT there is no need to target every cancer cell in the body in order to eradicate all spreading cancer cells. Also, the two genes are universal immune stimulatory genes that can be used to treat many types of cancers. Significantly, AMDL claims their CIT phase I clinical studies of ten patients indicated that these two genes and tumor cells carrying these two genes do not display toxicity. The combination of two genes formulates a synergistic force to induce a strong anti-cancer response which eradicates cancer. Finally, the approach is compatible with conventional chemotherapy and radiation therapy to exert a cooperative anti-cancer effect.

### AMDL Inc. and the Growing Market for Gene Therapy in China

In 2006 AMDL acquired Jade Pharmaceutical Inc. of Shenzhen China. Since that time AMDL has been aggressively moving forward with its plan to get the CIT gene therapy engaged in the approval process with the China SFDA. Cancer is the fastest growing disease in China and the number one cause of death. According to IMS Global Insights the Chinese cancer treatment market will be worth more than \$40 billion by 2008, driven by an ageing population, better diagnostics, and the introduction of further innovative products that have many years of patent protection ahead of them. AMDL will also benefit from the very active gene therapy research community and resources available in China. AMDL and their Chinese subsidiary Jade Pharmaceutical have held productive meetings with research labs and gene therapy innovators in Shenzhen and Beijing.