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Biotech Deals Put Lung Cancer Vaccine Hopes in the Hands of Japan Tobacco

This briefing documents the links between Japan Tobacco and drug development for two major smoking-related diseases – lung cancer and coronary heart disease. In particular, it covers financial agreements - based on patents and licences - between a number of biotechnology companies and the pharmaceutical division of Japan Tobacco. Payments of millions of US dollars are involved.

The agreements include:

1. An exclusive licence given by US biotech company **Corixa** to Japan Tobacco to develop and market future Corixa lung cancer vaccines in North America, Japan and many other countries. Corixa and Japan Tobacco hope to develop these vaccines from Corixa's patented human genes and associated technologies.
2. A collaboration agreement between US gene therapy company **Cell Genesys** and Japan Tobacco covering Cell Genesys' genetically engineered lung cancer vaccines. The agreement gives Japan Tobacco sole marketing rights for these vaccines in Japan, Taiwan and Korea, and shared marketing rights in the rest of the world outside the US. The vaccines are currently undergoing clinical trials in the US.
3. Past payments from Japan Tobacco to **British Biotech** relating to the development and testing of a genetically engineered protein to treat cardiovascular diseases, including heart attacks and strokes.

GeneWatch's key concerns regarding these agreements are:

- **The role of Japan Tobacco:** Smoking is a key cause of cancer - particularly lung cancer - and cardiovascular disease. The most effective way of preventing many cancer and

heart-disease deaths is by government controls on the tobacco industry, such as banning tobacco advertising. Japan Tobacco profits from tobacco sales, opposes "over-regulation", and now hopes to exploit the patenting and licensing system to profit from selling treatments for the major smoking-related diseases that its products cause.

- **Profiteering from the gene patent system:** The deal between Corixa and Japan Tobacco is related to patent claims by Corixa on human gene sequences combined with an exclusive licence. This system means that others can be prevented or hindered from developing similar treatments, high prices can be charged for any vaccine developed under the sole control of Japan Tobacco, and the free exchange of information and materials with other researchers can be blocked. Anyone challenging the patents or licence would face a costly and expensive legal battle. The deal between Cell Genesys and Japan Tobacco is also based on an exclusive licence which will give Japan Tobacco sole control over prices for the vaccine in many countries.
- **Abuse of donated tissue and public trust:** Development of the vaccines relies on volunteers donating tissue samples for research and taking part in clinical trials. Much of the initial research is publicly funded in universities and institutes. Volunteers (and many of the researchers) are likely to be unaware that a tobacco company has control over the future development and marketing of any treatments that may result or that a tobacco company will be making profits from these treatments. The patents that allow this to happen do not name Japan Tobacco. Instead they name biotech companies, individuals, universities and institutes who have then made the licensing deals.

- **Potential for false hope and exaggerated claims:** Huge difficulties remain in producing effective cancer treatments. Future marketing of lung cancer vaccines by Japan Tobacco could create false hope that a cure for cancer is just around the corner and be counter-productive in encouraging smokers to give up.

There are no safeguards in place to prevent more such licensing deals as the number of patents on gene sequences increases. The recitals (introduction) to the 1998 European Directive on the legal protection of biotechnological inventions state that: *“if an invention is based on biological material from a person, then they must have had an opportunity to express free and informed consent before a patent is granted”*. However, the recitals are not legally binding and the UK Government has chosen not to implement any such consent requirement in UK law.

Who is Japan Tobacco (JT)?

JT International¹ was formed when the Japan Tobacco Group purchased the international operations of R J Reynolds Inc. in 1999. It is the world's third largest international tobacco company, manufacturing three of the world's top five cigarette brands - **Camel, Mild Seven and Winston** - plus the menthol brand, Salem. JT sold almost 450 billion cigarettes during the financial year ending 31st March 2001 with total net tobacco sales of US \$33.4 billion.

Japan Tobacco entered the pharmaceutical business in 1987. As well as selling a range of pharmaceutical products, it has launched an anti-HIV drug in Japan and is developing anti-diabetic and anti-inflammatory agents. However, JT remains first and foremost a tobacco company - net sales for JT's pharmaceutical division in the 2000/2001 financial year were around 1.6% of tobacco sales.

In common with the rest of the tobacco industry, JT opposes what it sees as “over-regulation”. For example, Japan Tobacco Inc. and JT International recently launched a legal challenge against the EU Tobacco Directive² and a branch manager of Japan Tobacco reportedly made a speech earlier this year denouncing Japan's tobacco control plan as “fascism”³.

Biotech Deals with Japan Tobacco

1. Corixa Corporation (www.corixa.com)

The Company

Corixa Corporation is based in Seattle, Washington. It describes itself as *“committed to treating and preventing autoimmune disease, cancer and infectious disease by understanding and directing the immune system”*⁴.

The Product

Corixa's deal with Japan Tobacco relates to the lung cancer vaccines it is developing using DNA and proteins found in human lung tumours. Corixa's vaccine is intended to use certain proteins found in lung tumours to generate an immune response in the patient so their own immune system would then destroy the tumour. The proteins would be produced synthetically or by using genetically engineered cells (such as yeast) in which human DNA that produces such proteins has been inserted. Substances which boost the immune system may also be included in the vaccine.

The Deal

In 1999, Corixa Corporation granted Japan Tobacco a 3-year exclusive licence to develop and sell vaccine and antibody based products aimed at the prevention and/or treatment of lung cancer (and potentially other cancers) in North America, Japan and many other countries⁵. The licence excludes Europe, the former Soviet Union, Argentina, Brazil and Columbia, which are covered by another exclusive licence granted by Corixa to an Italian multinational pharmaceutical company (Zambon Group, www.zambongroup.com). Japan Tobacco and Zambon Group have been given a co-exclusive licence to develop and sell lung cancer vaccines in China.

The Payments

Under the two agreements with Zambon Group and Japan Tobacco, Corixa expects to receive over \$40 million in licence fees, research funding and milestone payments if it makes successful clinical and commercial progress with the vaccines. Corixa made \$1.6 million from its deal with Japan Tobacco in 1999⁶. Total revenue from the combined agreement with Zambon and Japan Tobacco was \$4.7 million in 1999 and

\$6.7 million in 2000⁷. Corixa received a \$1m milestone payment from Japan Tobacco in July 2001⁸.

The Patents

In April 2001, Corixa was granted a US patent (US6210883) which claims potential lung cancer vaccine methods but not the lung cancer genes themselves. However, since 1998, Corixa has filed a group of 6 related world patents (WO0100828, WO0065053, WO0061612, WO0060077, WO9947674, WO9938973), some of which include claims for human lung tumour gene sequences. In one patent, gene sequences come from lung cancer cells provided by two patients (Example 1, WO9947674). The DNA from these patients was then compared with DNA from four normal human lung samples. In another patent, tumour and normal tissue samples are used from a single patient with lung cancer (Example 1, WO9938973). The patents do not reveal whether the lung cancer patients were smokers. The patients may or may not know that Corixa is patenting their gene sequences, but it seems unlikely that they were aware of Corixa's licensing deal with Japan Tobacco.

2. Cell Genesys (www.cellgenesys.com)

The Company

Cell Genesys is based in Foster City, California. It describes itself as a leading gene therapy company, focused on the development and commercialisation of cancer vaccines and gene therapies to treat major, life-threatening diseases. Cell Genesys has the largest patent portfolio in the gene therapy field. In July 2000, it had more than 235 patents issued and 330 pending⁹.

The Product

Cell Genesys' deal with Japan Tobacco relates to the use of its genetically engineered GVAXTM vaccine to treat lung and prostate cancer. Cell Genesys acquired the GVAXTM cancer vaccine when it merged with Somatix Therapy Corporation in 1997¹⁰. Cell Genesys is currently conducting clinical trials for its GVAXTM vaccines for prostate, pancreatic and lung cancers and myeloma. A trial for leukaemia is also planned. The vaccines use genetically engineered cancer

cells intended to boost the patient's immune system.

The Deal

In late 1998, Cell Genesys Inc. announced the signing of a worldwide collaboration with Japan Tobacco Inc. regarding the development and marketing of its GVAXTM cancer vaccine¹¹. The agreement initially covered the use of the genetically engineered vaccine to treat prostate cancer and another unnamed cancer. This was later identified as lung cancer¹². The deal involves the companies sharing equally in product development costs and future profits. Japan Tobacco was given sole marketing rights in Japan, Taiwan and Korea and an equal share in marketing rights elsewhere, with the exception of North America.

The Payments

The agreement provided for a \$12.7 million payment from Japan Tobacco on signing, followed by a first anniversary payment of \$2.5 million. Cell Genesys predicted it could receive up to \$27.5 million in research and development funding in the first three years and around \$80 million in milestone payments if the collaboration continued. Loans of up to \$30 million were also agreed for Phase III trials of the cancer vaccines should the collaboration continue¹¹. Cell Genesys received a \$4.5 million milestone payment from Japan Tobacco in 1999 following completion of an initial Phase I/II clinical trial for lung cancer vaccine. A \$6 million milestone payment followed in 2001 for the completion of the first Phase II clinical trial for prostate cancer vaccine¹³.

The Patents

In 1999, Cell Genesys announced it had been issued a second broad US patent (US5904920) for its GVAXTM cancer vaccine technology¹⁴. However, this patent and an earlier related one (US5637483) do not list Cell Genesys as either applicant or inventor. The named applicants are the Whitehead Biomedical Institution and John Hopkins University Medical Institute and the named inventors are Glenn Dranoff, Drew Pardoll and Richard Mulligan. Other related US patent applications have not yet been granted.

The genetic vaccine was first developed and tested in animals in 1989 by Drew Pardoll and

other researchers at Hopkins. Glenn Dranoff (Dana Farber Cancer Institute) and Richard Mulligan (Harvard University) identified the immune system activating gene used in the vaccine¹⁵.

The nature of the commercial relationship between Cell Genesys and the named institutes and individuals on the patents is unclear. Glenn Dranoff, assistant professor of medicine at the Dana-Farber Cancer Institute and Harvard Medical School, has been conducting the lung cancer vaccine trials at Harvard¹⁶. Glenn Dranoff is one of two named inventors on Cell Genesys' more recent world patent WO0072686. This patent, dated December 2000, claims methods for stimulating an immune response using genetically engineered cancer cells and describes in detail a clinical trial using genetically engineered lung cancer cells as a vaccine in 24 patients (Example 1).

It is unclear whether any of the individual researchers or institutes involved are aware of Cell Genesys' deal with Japan Tobacco for the development and marketing of these vaccines.

None of the above patents claim gene sequences.

Other Links with Japan Tobacco

Cell Genesys has a number of other links with Japan Tobacco. These agreements do not involve specific treatments for smoking-related diseases.

In 1991, Cell Genesys and JT Immunotech USA Inc (a wholly owned subsidiary of Japan Tobacco Inc.) established Xenotech, a worldwide equally-owned joint venture working on human antibody research. Options for exclusive rights to market human antibody products were granted to Japan Tobacco as part of a further agreement in 1994¹⁷. The research collaboration was extended for a further two years in 1995¹⁸. Japan Tobacco sold its interest in Xenotech to Abgenix Inc. (www.abgenix.com) in 1999 but Abgenix and JT also concluded a separate licence agreement which allowed JT to use Xenotech's technology and continue to commercialise human antibodies obtained from it¹⁹.

Cell Genesys continues to hold a 10.5% stake in

Abgenix Inc, its former subsidiary, which is collaborating with Japan Tobacco on the development of a human antibody treatment for psoriasis²⁰. An agreement between Japan Tobacco and Cell Genesys when the latter was launched in 1996 included options giving Japan Tobacco exclusive licences to market selected Abgenix products in some countries²¹. Abgenix is developing antibodies for inflammation and for cancer.

Cell Genesys and Japan Tobacco also jointly supported the first clinical trial of gene therapy in Japan, using the GVAX™ vaccine for kidney cancer¹¹.

3. British Biotech (www.britbio.co.uk)

The Company

British Biotech, based in Oxford, is researching and developing products for treating cancer and cardiovascular disease and new antibiotics. It stopped developing its most advanced cancer treatment product "marimastat" in 2000 after it failed clinical trials for lung cancer²².

The Product

British Biotech's B-10153 is a genetically engineered protein that has shown thrombolytic (clot-dissolving) and anti-thrombotic (clot-prevention) properties. It has potential use in the treatment of cardiovascular diseases including heart attack and stroke. According to British Biotech, B-10153 has obtained broad patent coverage and a Phase II trial is planned in 2002²³.

The Deal

British Biotech received £0.5 million from Japan Tobacco Inc. in the financial year ending 30th June 1999 following completion of the Phase I study of its product B-10153²⁴.

B-10153 is now available for licence/collaboration with British Biotech actively seeking a marketing/development partner²⁵. It therefore seems unlikely that Japan Tobacco remains involved.

The Patents

Since 1991, British Biotech has filed four world patents relating to its clot-dissolving and clot

prevention technology. It was granted 2 related US patents in 1997 (US5637492 and US5645883) and one in 1999 (US5932213). The patents include claims for genetically modified gene sequences.

4. Other Biotech Alliances

Japan Tobacco has other biotech alliances with Tularik Inc (obesity, diabetes, orphan nuclear receptors, pharmaceuticals research), Gene Logic Inc (renal disease and “an undisclosed therapeutic area”), Pharmacia (diabetes) and Chiron Corporation (Hepatitis C).

Conclusions

Smokers are at an increased risk of more than 50 illnesses of which 20 can be fatal. In countries where cigarette smoking has been common for several decades, about **90% of lung cancer**, 15-20% of other cancers, 75% of

chronic bronchitis and emphysema, and **25% of deaths from cardiovascular diseases at ages 35-69 years** are attributable to tobacco. Lung cancer is the most common form of cancer. In developing countries, smoking causes about 10% of cancer deaths²⁶. Controls on tobacco can save huge numbers of lives – for example, the UK Department of Health estimates that a UK tobacco advertising ban could eventually save up to 3000 lives a year²⁷.

Allowing a tobacco company to profit from selling treatments for a disease which is caused by its own products is clearly unacceptable. Giving Japan Tobacco exclusive rights over the development of lung cancer vaccines will also hinder other researchers from developing similar treatments. Unless companies are prevented from patenting gene sequences, such licensing agreements will enable them to profit financially at the expense of medical research and therefore to the detriment of those who suffer from serious diseases.

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