Storm warnings for p53

The use of tumor suppressor genes, particularly *p53*, as a new therapeutic approach for treating cancers has captured the imagination not only of the scientific and medical community, but also of Wall Street and venture capitalists. With *p53* as their technology bellweather, a few biotechnology companies are aggressively pursuing therapeutic strategies for eradicating cancerous cells that carry mutant *p53* genes. However, questions about the ownership and patent rights of the *p53* gene are placing companies on a legal collision course.

Both Canji, Inc. (La Jolla, California) and Introgen, Inc. (Austin, Texas) are using a gene therapy approach to cancer. Both companies are inserting wild-type *p53* into solid tumors to correct for the gene defect, while increasing the tumor cells' susceptibility to chemotherapeutic agents and, subsequently, to cell death. In a related but novel approach, aimed at circumventing some of the intellectual properties and technical hurdles associated with *p53* gene therapy, Onyx Pharmaceuticals, Inc. (Richmond, California) is using genetically engineered viruses to infect and kill cancer cells that express mutant *p53* protein.

Jack A. Roth from M.D. Anderson Cancer Center in Houston, Texas, and a scientific founder of Introgen, has been leading the clinical effort to correct the genetic defect in lung cancers by injecting wild-type *p53* in a retroviral vector. Supported by Introgen and its joint-venture partner Rhône-Poulenc Rorer, Roth and colleagues are conducting phase I/II clinical trials using wild-type *p53* gene therapy for non-small cell lung cancers (see *Nature Medicine* 2, 985-991; 1996). In expanding its clinical development programs, Introgen and its investment bankers are in the process of raising US\$20-\$30 million from the public equity market by selling 3.2 million shares of its common stock in an initial public offering.

Utilizing Canji's technology, Schering-Plough is also entering the clinic, treating liver cancers that have evolved secondarily to colon cancer with wild-type *p53* in an

adenovirus vector. Last December, privately held Canji was acquired by Schering-Plough for over US\$54 million.

Last May, the US Patent and Trademarks Office issued a patent to Canji covering the methods and use of tumor suppressor genes, with specific claims for the use of *p53* gene in gene therapy. The issued patent has a priority date of August 1990 as a continuation in part of an umbrella patent, which has not yet been issued, covering tumor suppressor gene therapy with a filing date of October 1988. The University of California, San Diego, licensed the patents to Canji in 1990 with Wen-Hwa Lee and collaborators as the inventors of the technology.

Since intellectual property is one of the cornerstones for drug development, a patent conflict could be in the offing between Schering-Plough and Rhône-Poulenc Rorer in the use of *p53* for gene therapy. Schering-Plough owns the use patent for *p53* with its broad claims in the USA as well as a patent being granted by the European Patent Office. With its own patent claim not clearly defined for *p53*, RPR may be faced with the difficult task of converting Introgen's technology to a commercial product. With tens of million of dollars being poured into the *p53* gene therapy programs, both pharmaceutical giants may be poised to engage in a bitter patent infringement battle soon; particularly if *p53* gene correction actually works.

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AMA spends money with the big boys

Over the past two years the American Medical Association and the tobacco industry have stepped up their fight over the regulation of tobacco. While the two groups appear to have little in common, they do share two things that matter very much in Washington, DC — power and money. Because new rules require that anyone who lobbies Congress must disclose twice a year how much they spent on items like salaries, lunches, entertainment and other incidentals, recently released documents show just how much congressional influence costs.

For the first half of 1996, tobacco conglomerate Philip Morris spent more than US\$11 million lobbying the federal government, more than any other organization. The AMA, which spent nearly \$9 million, came in second. The US Chamber of Commerce, General Motors, and the Christian Coalition round out the top five.

"These [disclosures] show just how much is at stake lobbying [Congress] and how much people are willing to spend to get their message across," said Christopher Deering, associate professor of political science at George Washington University. "Overall, this law has

been a success to the extent that it has made the lobbying process fairly transparent."

Although the AMA listed several tobacco-related causes among the issues on which the organization spent lobbying money from January to June 1996, they were but a small fraction of the AMA's efforts. AMA lobbyists worked on a variety of Medicare and Medicaid bills, legislation to change medical malpractice laws, and a number of anti-managed care measures. The anti-managed care provisions included one that would require insurers to pay for a minimum 48-hour stay in a hospital for new mothers who have a normal vaginal birth and 96 hours for a cesarean section. That bill was signed into law in September. However, the AMA lost a battle last month to pass a provision that would prohibit managed care plans from limiting physician-patient communications.

The new disclosures were required under a lobbying reform act passed by Congress in 1995 and offer a first glimpse into what has always been a closely guarded secret — the strategies and finances of some of the most influential special interests in Washington.

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Lobbying expenses for selected groups, January through June 1996

Organization	Total (\$US)
Philip Morris	\$11,300,000
American Medical Association	\$8,700,000
U.S. Chamber of Commerce	\$7,500,000
General Motors	\$6,900,000
Christian Coalition	\$5,900,000
Pfizer	\$5,000,000
Pharmaceutical Research & Manufacturers of America	\$3,350,000
American Society of Internal Medicine	\$840,000
American Association of Family Physicians	\$510,000
Association of American Medical Colleges	\$450,000
American College of Physicians	\$180,000

Source: Federal Lobbying Disclosure Act filings. U.S. House of Representatives.