Promising drug is victim of bad business

It's disappointing to see any medicine fail in clinical trials: patient hopes are dashed, drug companies lose out on their investment and scientists have to return to the drawing board. The setback in trials of colon cancer drug Erbitux provides a poignant example of the first two conditions, but, conversely, it is also an example of successful biomedical research.

Erbitux, also known as C-225, was developed by

New York-based ImClone Systems and, after demonstrating strong potential in Phase II trials, was backed last September by pharmaceutical giant, Bristol-Myers Squibb (BMS) in a record-setting \$2 billion licensing deal.

On 28 December, ImClone announced on that it had received a 'refusal to file' letter from the US Food and Drug Administration (FDA), and claimed that the letter merely requested additional documentation from the drug's earlier clinical trial. But alleged excerpts from the document, published in *The Cancer Letter* (4 January 2002) contradicted that view, suggesting instead that an entirely new trial was required, and that ImClone had known for over a year that its proposed trial would not meet FDA standards.

Investors were startled and more bad news followed. In late January, ImClone announced that it was the target of investigations by the US Securities and Exchange Commission, the Department of Justice, and a Congressional subcommittee, and nearly two dozen class-action lawsuits have been filed by shareholders accusing flamboyant CEO Sam Waksal and his brother Harlan of insider trading and fraud.

Some ImClone board members, including the president of the M.D. Anderson Cancer Center in Texas, John Mendelsohn, also served on the board of the troubled Houston energy company Enron, thus thrusting ImClone's troubles into the spotlight of a major political scandal. Last month, BMS was fighting to restructure its deal and to oust the Harlan brothers. ImClone shares have sunk from an early December high of \$75 to around \$17.

Ironically, Erbitux may be a victim of its own potency. The drug is a hybrid monoclonal antibody against epidermal growth factor receptor (EGFR), a signaling receptor

required for growth by many types of cancer cells. Erbitux appears to prevent tumor growth by blocking EGFR. In the Phase II trial that formed the basis of ImClone's FDA application, patients who had failed to respond to the established chemotherapy drug irinotecan, received a combination of irinotecan and Erbitux. And because of irinotecan's high toxicity, the FDA seems to have requested a large-scale trial using Erbitux alone.

But having Erbitux show efficacy by itself would be bad business for ImClone. "Genentech has a patent that basically covers any chimeric antibody [used by itself]", explains Jason Zhang, an analyst at Stephens Inc. However, ImClone holds a patent for combination treatments using

an anti-EGF antibody with chemotherapy, so "if they prove this combination therapy works they will probably make a strong argument that they are not infringing Genentech's patent." However, licensing the monotherapy patent from Genentech—which is developing competing EGFR-targeting drugs—could cost ImClone dearly.

Several oncologists who have conducted trials for ImClone declined to comment on the record, but some told *Nature Medicine* that recent news about the company's alleged bad business practices is eroding the credibility of clinical research. One scientist, speaking on condition of anonymity, summed up the prevailing view: "EGFR is an exciting area and this drug clearly has clinical activity. It's a shame that all this controversy, much of it outside the realms of the clinic, will derail the path of a drug which could have such benefits for the patients."

Alan Dove, Philadelphia

ImClone share price over the past year

Set back to Alzheimer vaccine studies

Elan, the Ireland-based biotechnology company that had taken the lead in developing a potential vaccine to treat Alzheimer disease, has suffered a double set back. Within days of announcing that trials of its therapeutic vaccine, AN-1792, had been suspended, the company's share value plummeted by over 70% amid concerns over accounting practices and calls for Elan directors to resign.

AN-1792 was undergoing Phase IIa trials in Alzheimer 360-patients, which were supported by the large vaccine manufacturer, Wyeth-Ayerst. However, five subjects (four in France and one in Switzerland) showed signs of inflammation of the central nervous system. Presently it is not known how this adverse reaction was picked up, although this could have been indicated by headaches and an increased state of confusion of patients.

A company spokesperson told *Nature Medicine*, "The trial has been suspended while an independent safety monitoring commission finds out exactly what caused these side-effects. The investigation is being carried out between dosing sched-

ules. This will give the committee enough time to find out whether the vaccine is indeed the cause, and will not disrupt the trial if the vaccine is given the all-clear."

One theory for the cause of Alzheimer disease—the inflammation hypothesis—is that deposits of β -amyloid elicit a non-specific immune response that activates microglia to become autotoxic and destroy surrounding neurons, resulting in cognitive decline.

AN-1792 causes the immune system to create antibodies against β -amyloid, and there are currently two potential mechanisms for its effect under debate. First, that antibody binds to β -amyloid deposits and activates the complement system, which in turn

triggers receptors on microglial cells to begin removing the debris. A second possibility is that the AN-1792 protein dissolves the plaque directly. This would release monomeric β -amyloid peptide, which might again cause activation of microglia through RAGE or scavenger receptors on the surface of these cells.

Some scientists say that by the nature of

Elan share price plummets