Cancer Pathways' target not validated by clinical results

A preliminary evaluation of unblinded data from Cell Pathways' (Horsham, PA) pivotal phase III trial of its lead product, Exisulind, for cancer "suggests that the study did not achieve a statistically significant clinical response when compared to placebo," the company announced in February. The unfavorable results prompted a two-thirds drop in share price—correlating with a $435 million loss in valuation—in the first day of trading following the announcement. The fact that Cell Pathways, which has no track record, no corporate collaborator, no product on the market and only a single phase III clinical trial of its first product, was able to lose such an amount of money indicates the degree to which investors had bid up the value of its as-yet-unproven technology and how much that confidence has been dented.

Cell Pathways has no immediate explanation for the unexpected trial results and plans to analyze the data in detail in the coming weeks. The results are "totally inconsistent with all of the data previously generated in humans and in animal models and tissue culture," says Bob Towarnicki, CEO of Cell Pathways.

The company's disappointment is further compounded by its belief that Exisulind will exhibit antitumor effects in a range of cancers. This belief has been based on observations that inhibition of the drug's putative target, a novel phosphodiesterase (PDE), triggers apoptosis specifically in tumor cells. Recent patents awarded in Europe and the United States describe this mechanism, but only in general terms. Cell Pathways has publicly stated that it has plans to disclose the specifics of its understanding of the drug's mechanism of action in scientific and clinical meetings later this spring.

The company believes Exisulind's target to be a member of the PDE5 family. However, there is no additional evidence to suggest PDE5 is a cancer target and, apparently, no other companies are working on PDEs in cancer. (The only known inhibitor of PDE5 is sildenifil (Viagra), a vasodilator that acts on a different isoform, found in smooth muscle.) Indeed, reviewing Cell Pathways' US patent several days before the phase III announcement, the head of R&D at one biotechnology company, who prefers to remain anonymous, pointed out that it does not answer the question whether PDE5 is an important target for cancer—a claim that the pivotal clinical data from Exisulind has so far failed to validate.

The phase III trial—for the treatment of patients with adenomatous polyposis coli, a precancerous condition of the colon—appeared to be the most likely setting in which to demonstrate proof of principle. The results apparently came as a genuine surprise to management, especially given Exisulind's development history.

That history had shown that Exisulind is the sulfone metabolite of sulindac, a nonsteroidal anti-inflammatory drug (NSAID), made by Merck (Whitehouse Station, NJ), that has demonstrated efficacy in treating precancerous polyps. However, sulindac, like other NSAIDs, acts on the co-oxygenase (COX) pathways, COX-1 and COX-2, resulting in gastrointestinal side effects that make it inappropriate for chronic administration.

Gastroenterologist Rifat Pamukcu, now Cell Pathways' chief scientific officer, had used sulindac successfully in colon cancer patients while an assistant professor of medicine at the University of Cincinnati. He then demonstrated that sulindac's sulfone metabolite, which does not interact with COX pathways, exhibits broad-based antitumor activity in cell lines and anticolon cancer effects in rats.

The link to PDE came a few years later, after Pamukcu had cofounded Cell Pathways along with Floyd Nichols, one of the colon cancer patients he'd treated with sulindac. "We found PDEs in high levels in colon cancer," Pamukcu explains, "re-ran the PDE assays with Exisulind (the sulfone metabolite), and found it to be a potent inhibitor in the same IC_{50} range in which we were seeing cell kill."

Further encouragement came while looking at different PDE isozymes for specificity. The researchers found that while Exisulind mildly inhibited PDEs, it strongly inhibited cGMP-PDE in cancer cells, "suggesting that Exisulind treatment related to neoplastic transformation [tumor alteration]." According to Pamukcu, elevated levels of cGMP-PDE cause degradation of cGMP, aborting the apoptotic pathway. Exisulind, he says, dropped cGMP-PDE to levels found in normal mucosa. "We then clearly thought we had an inducible enzyme."

Although the company believes cGMP-PDE is a member of the PDE5 family, Thompson points out that different PDE isoforms are found in different tissues: In conferring selectivity (and specificity), "it's the enzyme that counts," he says, not the inhibitor. Cell Pathways is using structure–activity data from Exisulind and its target to develop second-generation compounds with antineoplastic activity. It filed an investigational new drug application in December 1998 to begin clinical trials with the first of these, CP461. Pamukcu claims CP461 is one to two logs more potent, and much less toxic, in animal studies, than Exisulind.

In the meantime, Cell Pathways still "firmly believes in [Exisulind's] potential to treat precancerous and cancerous lesions" and is committed to continuing clinical trials. It expects to report interim data from a phase II trial of Exisulind in prostate cancer this month.

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Pharma strategies extend drug lives

The pharmaceutical industry is facing the expiration of patents to more than 30 blockbuster drugs by the year 2002. With the threat of cheaper, generic drugs taking market share, several pharmaceutical companies are implementing various legal strategies to delay the inevitable loss of patent rights. Stop-gap tactics—such as patent infringement litigation, the filing of secondary or blocking patents, and licensing rights to newer, improved drugs—are effectively buying companies more time to continue collecting billions of dollars in revenues. As a result, biotechnology companies, many of which are developing purer forms of drugs, novel forms of drug delivery (*Nat. Biotechnol.* **16,** 115, 1998) or pharmacogenomic-based diagnostic tools (*Nat. Biotechnol.* **15,** 829, 1996), could end up winners.

Eli Lilly & Co. (Indianapolis, IN) is fighting to protect $3 billion annual sales of its selective serotonin re-uptake inhibitor, Prozac (fluoxetine). In a $4 million settlement in January, Lilly won a three-year, two patent infringement, lawsuit against three generic drug companies: Barr Laboratories (Pomona, NY), Apotex (Toronto, Canada), and Geneva Pharmaceuticals (Broomfield, CO). This ensures, in the absence of an appeal and any other litigation, that Prozac will not become a generic drug until December 2003.

In addition, new patent life for the antidepressant is guaranteed until 2015 as a result of a $90 million agreement in December 1998 with Sepracor (Marlborough, MA) to develop an improved, purified isomeric form of the drug. The deal calls for Lilly to bear the