Companies race to develop first Hedgehog inhibitor cancer drug

ORLANDO, FLORIDA — Basal cell carcinoma is the most common form of skin cancer, but in people with a hereditary predisposition to this disease, lesions crop up so fast that they can hardly keep pace with their doctor's appointments. "Surgery can become tedious, and often, because of that, people don't go as often as they should and the [cancerous] areas grow larger," says Maria Michalowski, a former board member of the Basal Cell Carcinoma Nevus Syndrome (BCCNS) Life Support Network who herself suffers from the disease.

Yet, judging by trial results reported here last month at the annual meeting of the American Association for Cancer Research (AACR), pharmaceutical options on the horizon may preclude the need for regular surgery. In a phase 2 study of 41 people with BCCNS, a team led by Ervin Epstein from the Children's Hospital Oakland Research Institute in California found that participants taking an experimental Genentech drug called vismodegib developed only four new tumors on average over the course of a year, compared to 24 in subjects on placebo. Plus, subjects taking the drug saw their existing skin lesions shrink dramatically, whereas those on the dummy pill experienced modest growths. "Indeed, there was a tremendous reduction in new lesions," says Epstein. "The people on the drug had no surgeries. The difference was dramatic."

Vismodegib, also commonly referred to as GDC-0449, works by inhibiting signaling in the so-called Hedgehog pathway, which regulates cell growth and differentiation. Mutations in this pathway are responsible for some cases of BCCNS as well as a form of brain cancer known as medulloblastoma. And, indeed, vismodegib has also been shown to benefit a young man with the latter disease (*N. Engl. J. Med.* **361**, 1173–1178, 2009).

Picture of lily: Cyclopamine's source.

But even when no such mutations are present, aberrant Hedgehog signaling can still drive solid tumors, for example by supporting the blood vessels that fuel their growth. That's why Genentech, a San Francisco–based subsidiary of the Swiss pharma giant Roche, is currently testing its drug for nearly 20 other types of cancer.

The phase 1 data from a range of solid tumors, published last month, look promising (*Clin. Cancer Res.* **17**, 2502–2511, 2011). "If this drug is helpful for other diseases, we want to figure that out, too," says medical oncologist Jennifer Low, who leads Genentech's global development for vismodegib.

Genentech's compound is not the only Hedgehog inhibitor in clinical development, though. At the April meeting, researchers from a handful of other drug companies, including Pfizer, Takeda, Novartis and Infinity, presented phase 1 or preclinical data from their own experimental drugs, all of which target the Smoothened protein, a key component of the Hedgehog signaling pathway.

According to Philip Beachy, a molecular biologist at Stanford University School of Medicine in California who first cloned and characterized the gene encoding Hedgehog in fruit flies in the early 1990's, the reason why so many companies are developing Hedgehog inhibitors is because "this pathway is easily druggable."

Spiked pathway

In 1998, Beachy and his colleagues first showed that a compound derived from the corn lily plant called cyclopamine worked by blocking the Hedgehog pathway (*Science* **280**, 1603–1607, 1998). Four years later, his team identified four small molecules that inhibit Hedgehog activity but are structurally distinct from cyclopamine (*Proc. Natl. Acad. Sci. USA* **99**, 14071–14076, 2002).

Then big pharma clued in. "All the drug companies caught on to this and realized it's easy to hit this pathway," says Beachy.

Eli Lilly is one such company. At the meeting last month, scientists from the Indianapolis, Indiana–based drugmaker presented preclinical data showing that its drug, called LY2940680, inhibits cancer growth in cell lines containing a mutation in the gene encoding Smoothened that researchers had previously observed in a patient with cancer who developed resistance to vismodegib (*Science* **326**, 572–574, 2009). "Part of our differentiation strategy to improve benefit in the patient population we aim to treat is demonstrating activity of our preclinical molecules at that clinically observed mutation," says Jonathan Yingling, vice president of oncology research at Lilly Research Laboratories. The drug is currently being tested in phase 1 trials for people with a range of solid tumors.

Infinity Pharmaceuticals, meanwhile, is advancing its own derivative of cyclopamine, known as IPI-926, with improved potency and stability. After completing a successful phase 1 trial of the drug in people with advanced solid tumors, including those with BCC, the Cambridge, Massachusetts biotech firm launched separate phase 2 trials in people with pancreatic cancer and with chondrosarcoma bone cancer. "The problem in pancreatic cancer is that drugs just can't reach the tumor cells," says Infinity's senior director of product development Margaret Read. She explains that IPI-926 changes the blood vessel support of the tumor to improve the delivery of other chemotherapeutic drugs. Although there are no Hedgehog pathway mutations seen in chondrosarcoma, the idea is to inhibit the pathway all the same to slow the cancer's growth. Currently, no drugs exist to treat this type of cancer.

Even with all the competition, Genentech's Low remains confident that her company's compound will be the first to market. "We've treated a lot more patients than [other companies] have for a longer period of time," she says. "We have a better characterized drug right now."

There is growing momentum. Two weeks before the AACR meeting, Genentech announced that vismodegib proved effective in a 'pivotal' phase 2 study of more than 100 people with either metastatic or nonoperable BCC. Because no approved therapy exists for this patient population, "the plan is to file that data" for regulatory approval before the end of the year, says Genentech's vice president of molecular biology Frederic de Sauvage.

Vismodegib "is life changing," says Kristi Schmitt Burr, executive director of the Ohio-based BCCNS Life Support Network, many of whose members who have participated in Genentech's trials. "We have people crying because they're so happy... We feel like we're held hostage by this condition, and this removes the shackles."

Elie Dolgin