Hedgehog Drugs Begin To Show Results

By Ken Garber

When researchers announced last month that a hedgehog pathway inhibitor from Genentech had shown activity in a phase I cancer clinical trial, few noticed. Phase I results are usually suggestive at best. But in this trial, eight of nine patients with advanced basal cell carcinoma responded to the Genentech drug, and all eight are still enrolled 16 months into the study. “The first patient in the world gets treated with an inhibitor of this pathway and has a dramatic response,” noted principal investigator Daniel Von Hoff, M.D., of the Translational Genomics Research Institute in Phoenix, Ariz., at the annual meeting of the American Association for Cancer Research. “That … is the essence of translational medicine.”

It was also probably the first time that a cancer drug specifically targeting a developmental pathway has shown activity in people. The hedgehog pathway is critical for embryonic and postnatal organ and tissue development, and the Genentech results validated, at least for now, the emerging concept of cancer as a disease of normal development gone awry. At least five drug companies are working on antitumor hedgehog pathway blockers, and the coming years will probably see more drug candidates make their debut in the clinic against many forms of cancer.

Making the Cancer Connection

The idea that tumors hijack normal developmental pathways for their own growth has taken hold in the cancer research community. In addition to hedgehog, developmental genes Notch and Wnt are also being targeted (see J Natl Cancer Inst 2007;99:1284–5). The hedgehog pathway was first identified in 1980 by Christiane Nüsslein-Volhard, Ph.D., and Eric Wieschaus, Ph.D., of the European Molecular Biology Laboratory in Heidelberg, Germany, after examining thousands of mutant fruit flies for developmental defects. (To them, the mutant fly larvae resembled hedgehogs.) Their work led to the 1995 Nobel Prize for physiology or medicine. In general, hedgehog signaling is responsible for tissue patterning during development, as when hedgehog expression at the limb buds determines where fingers will grow and when hedgehog in the developing spinal cord induces the formation of motor neurons.

The first evidence of a cancer link came in 1996 with the discovery that Gorlin syndrome, a rare condition marked by extensive basal cell carcinoma skin tumors, was caused by a mutation in Patched1, the hedgehog receptor. Gorlin syndrome patients also often develop medulloblastoma, a childhood brain tumor, and rhabdomyosarcoma, a muscle tumor. In the late 1990s, researchers led by Ariel Ruiz i Altaba, Ph.D., then at New York University Medical Center, found that most sporadic basal cell carcinomas have hyperactivated hedgehog signaling. And in 1999, three groups reported that hedgehog was crucial for development of the cerebellum, where medulloblastomas arise. Many activating mutations have since been found in both basal cell carcinoma and in medulloblastomas.

Although these aren’t common epithelial tumors like breast, prostate, and lung, they’re not trivial. Basal cell carcinoma is easily cured by surgery or radiation, but advanced recurring cases can be fatal. Treatment of medulloblastoma with surgery and either chemotherapy or radiation usually cures, but it causes serious side effects in children. “There’s such a great need, at least in some patients, for something new,” said Tom Curran, Ph.D., a brain cancer researcher at the Children’s Hospital of Pennsylvania in Philadelphia.

Beginning in the late 1990s, Curran and others began trying to target hedgehog to treat these tumors with the help of transgenic mouse models. A natural-product hedgehog pathway inhibitor called cyclopa mine pointed the way to new drugs. In the late 1990s, Philip Beachy, Ph.D., a developmental biologist at Johns Hopkins University in Baltimore, demonstrated that cyclopa mine blocked the hedgehog pathway, and in 2002, James Chen, Ph.D., a chemist in Beachy’s lab, showed that cyclopa mine did this by binding to smoothened, a key transmembrane protein in the pathway. This finding triggered a rush of drug company activity aimed at finding hedgehog pathway inhibitors targeting smoothened. Of these
inhibitors, Genentech’s compound, first made by Curis Inc. in Cambridge, Mass., is the furthest along in development. A semi-synthetic cyclopamine analogue from Infinity Pharmaceuticals, also in Cambridge, should start human trials later this year.

**Reality Check**

Now big pharmaceutical companies, including AstraZeneca and Bristol-Myers Squibb, are in on the hunt because these drugs might work for more common tumors. Beginning in 2002, researchers implicated hedgehog signaling in a variety of tumor types, including prostate, lung, pancreatic, stomach, and bladder cancers, as well as melanoma, glioblastoma, and multiple myeloma. “About one-third of total cancer deaths are caused by the cancer types in which current evidence implicates Hh [hedgehog] or Wnt pathway activity in most cases,” Beachy wrote in a 2004 article in Nature. Ruiz i Altaba wrote last year that the hedgehog pathway blockers could provide “a unified therapy for many human cancers of different grades.”

Could hedgehog inhibitors be broad-spectrum anticancer drugs? It’s possible. Unlike in basal cell carcinoma and medulloblastoma, the hedgehog pathway in other tumors is not activated by mutations but by hedgehog ligand, which binds to its receptor, Patched1. The ligand may be produced by the tumor cell and bound to receptors on the same tumor cell or on adjacent ones, creating a positive feedback loop and driving tumor growth. Or, as several groups recently reported, the ligand may instead bind to and activate the pathway in the adjacent stroma, or connective tissue, leading to the release of growth factors that stimulate tumor expansion.

Either way, “even when the cancer is not explicitly due to a hedgehog pathway mutation, it could ... be sensitive to hedgehog inhibition, which would be tremendous,” said Lee Rubin, Ph.D., Curis’s former chief scientific officer.

But, Rubin added, proof of hedgehog dependence in many tumor types is lacking. Hedgehog antagonists “could turn out to be useful in several different cancers,” he said. “But maybe not every single report you read in the literature will turn out to play out in the clinic.” Julian Adams, Ph.D., Infinity’s chief scientific officer, agreed. “To be frank, we were unable to reproduce the dramatic effects published in some of these papers,” he said.

Both Infinity and Genentech have developed their own cancer models of hedgehog activity, instead of relying on others’ reports, even when those reports appeared in high-profile journals. In vitro experiments are suspect because some researchers observe a loss of dependence on hedgehog signaling in culture. (Ruiz i Altaba, however, does see dependence.) And in reporting tumor regression in xenograft mouse model results, Curran said, “You have to be really careful with those studies to be really sure that you’re seeing a significant and specific effect.”

From their own studies, companies are now cautiously optimistic that several tumor types rely on hedgehog signaling. “Our approach will be likely to try to find those tumors that are exclusively dependent on the hedgehog pathway, or if they’re partially dependent, marry them to some chemotherapies,” Adams said.

**Bones and Brain Tumors**

With the major tumor types still unconfirmed, basal cell carcinoma and medulloblastoma remain obvious targets for antihedgehog drugs. On the basis of the phase I results, Genentech will be targeting advanced basal cell in phase II, in addition to metastatic colorectal cancer.

Medulloblastoma is a more complex story. In 2004, using a small-molecule hedgehog pathway inhibitor from Curis, Curran’s group eradicated brain tumors in a transgenic mouse model of medulloblastoma. “The compounds are remarkably effective,” Curran said. But when Curran’s lab later tested the drug in juvenile mice, they found permanent bone defects, including shortened bones and deformed joints, even after just 4 days of treatment. “We weren’t expecting such a dramatic side effect,” Curran said. “I thought the bone would remodel and recover from it. But it didn’t.” These discouraging results mean that children with medulloblastoma, treated with hedgehog inhibitors, could suffer permanent bone defects.

But Curran remains hopeful. “This is such a promising agent,” he said. “There must be a way around these problems.” It’s possible, he said, that humans won’t show the same side effects as mice or that neural-specific hedgehog inhibitors or other ways to protect bone during treatment might be found. Infinity is working on the problem.

“Another possible solution is to block the hedgehog pathway downstream of smoothened. James Chen, at Stanford, is looking for such compounds, including ones specific for Gli1, the transcription factor that probably accounts for most of the progrowth effects of hedgehog. Chen speculated that that Gli1-targeted compounds may spare children from bone defects because Gli1-knockout mice are normal.

More importantly, smoothened inhibitors such as cyclopamine and the Genentech and Infinity compounds won’t work against tumors with hedgehog pathway activating mutations at the level of smoothened or downstream. Gli1 inhibition is the ‘gold standard,’ and that is what we are focusing on,” said Ruiz i Altaba, who is now at the University of Geneva medical school in Switzerland.

But there are concerns about toxic effects. Hedgehog signaling is crucial for the viability of many normal stem cells and cancer stem cells, which may account for its cancer-promoting effect in many tumors. But it raises continued on page 697
the possibility that blocking hedgehog could be toxic to self-renewing adult tissues such as bone marrow, gut, and skin. So far, in adults at least, that hasn’t happened: Von Hoff reported only mild side effects in the basal cell trial, and Infinity’s animal studies have suggested that its drug is safe in the animals tested. This finding may be because normal stem cells activate other developmental pathways such as Notch and Wnt that compensate or because only active stem cells are affected by hedgehog inhibitors, leaving resting stem cells to replenish the stem cell population.

Clearly, the race for antihedgehog drugs will continue, with the Genentech trials just the beginning. “The pathways involved in development are so highly conserved [among organisms] that I can’t imagine that cancers wouldn’t somehow take advantage of those things to help them along,” said William Matsui, M.D., a cancer researcher at Johns Hopkins. “So it’s an exciting time … trying to merge the two areas of developmental biology and cancer.”