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Abstract: The article profiles the biotechnology company Receptor Biologix, which is attempting to develop an anti-cancer drug. One drug candidate, called Dimercept, is designed to couple with cancer cells, inhibiting signals that tell the cell to replicate, thus stemming the growth of cancer within a patient's body.

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Blockbuster Dreams

New understanding of the biology behind a successful cancer therapy may lead to a drug that can treat an array of solid tumors

From the time it was approved in 1998, Genentech's Herceptin--a drug in the vanguard of the first generation of so-called targeted therapeutics--has achieved an impressive track record for a subset of beast cancer patients. Some patients who take it live longer and the size of their tumors is kept under better control than if they had received standard chemotherapy alone.

To develop Herceptin, researchers at Genentech drew on investigations into the molecular workings of a cancer cell. Some breast cancer cells stud their exterior with a surfeit of receptors that join in pairs to trigger a cascade of signals that cause the cells to replicate uncontrollably, develop resistance to chemotherapy and encourage the growth of blood vessels that promote the spread of tumor cells.

But Herceptin (generically designated trastuzumab) is aimed only at 20 to 25 percent of breast cancer patients, those whose tumor cells bear excessive numbers of a receptor known as HER2 on the surface. It has not, moreover, been proved effective against other cancers. H. Michael Shepard, who headed the team at Genentech that developed Herceptin and who fought vigorously against efforts within the corporate ranks to kill the program, is now chief executive of a tiny start-up located less than a mile away from the biotech giant's South San Francisco headquarters. The company, called Receptor BioLogix, is trying to go Herceptin one better.

The Big Turnoff

SHEPARD RETURNED TO the business of researching receptors in 2003, after a post-Genentech hiatus that included stints at two small biotechs and time spent as a consultant advising venture capitalists on new deals. His first push in that direction, although he did not realize it at the time, was a message on his answering machine from a former Genentech colleague, John Adelman. He knew Adelman, who had become a professor at the Vollum Institute at the Oregon Health & Science University, from the nights the two spent biding their time in the Genentech parking lot while each waited for their respective laboratory gels to finish processing. In his message on the machine, Adelman carried on about a new protein that could be a cure for breast cancer. Dubious, Shepard decided not to return the call.

A mutual friend phoned later and urged Shepard to listen to Adelman's story. When Shepard phoned back, Adelman told him about Gall Clinton's laboratory at O.H.S.U., which had come up with a chemical compound that had some promising characteristics as a drug candidate. In the late 1990s a graduate student in Clinton's laboratory had found a distinctive form of the HER2 protein. Clinton and Adelman told the student, Joni Doherty, that the compound was an artifact and not worth researching further. Doherty disregarded the advice and sequenced the genetic

material that encoded the protein.

The sequencing showed that the protein actually resembled a small piece of the receptor component that protrudes from the cell, the extracellular domain. It lacked the section that resides inside the cell and snakes across the cell membrane. And it included something that, at the time, was startling: When a cell needs a given protein, it transcribes the corresponding gene into a single strand of RNA and splices. out copies of unneeded DNA segments termed introns. The resulting, spliced messenger RNA (mRNA) transcript then serves as the template for making the protein. Doherty's protein, though, contained a part encoded by an intron. At one time, scientists disparaged introns as "junk" DNA. The Human Genome Project, though, underlined that differential inclusion or exclusion of introns can enable single genes to give rise to more than one type of protein.

The O.H.S.U. researchers wanted to know more about the function of their odd protein. It was not a receptor, but it acted as a decoy that imitated an aspect of receptor behavior. Normally a cell gets a message to begin the process of replication after a receptor joins physically, or "dimerizes," to another receptor. This pairing, in turn, sets off the transmission of chemical signals that induce the nucleus to trigger cell division. The drug candidate, originally called Herstatin, is now named Dimercept because it "intercepts" dimerization. The molecule sidles up to a receptor. The amino acids coded by the intron appear to initiate contact. A tiny arm that sticks out laterally from the protein interacts with a similar protruberance on the receptor and prevents the receptor from joining to another, thereby inhibiting the cascade of signals. What is more, Dimercept has this same effect not only on HER2 but on other receptors in the same family (the epidermal growth factor receptor family): HER1, HER3 and, possibly, HER4. The protein, made naturally in humans, is present mostly in fetal liver and kidney tissue, leading to the conjecture that it serves as a growth inhibitor in early development.

The ability to damp the activity of the entire complex of HER receptors explained the over-exuberance of the message on Shepard's answering machine. Inhibiting all four receptors could in theory provide treatment for a population of breast cancer patients that does not respond to Herceptin as well as for patients with other types of solid tumors that emerge anywhere from the lung to the pancreas to the brain.

Pharmaceutical companies found out about the compound through published papers and patents. But O.H.S.U. decided initially not to license the compound. It was still smarting from being unable to share in the sales revenues for Gleevec, the blockbuster anticancer compound owned by Novartis Pharmaceuticals but co-developed with O.H.S.U. researcher Brian Druker. So, with the university's blessing, Adelman made the call to Shepard, who agreed to take on the task of starting the company in 2003 and who raised early seed funding.

Good Pickings

LAST YEAR Receptor BioLogix brought in more than $33 million, an especially large take for a biotech start-up, particularly one with a drug that has not reached human clinical trials. The job at Receptor BioLogix is not unlike the one Shepard performed at Genentech, although now he has

responsibility for an entire operation. He is currently charged with transforming Dimercept from a laboratory curiosity to a drug ready for human clinical trials.

Although Dimercept stoppers the HER2 receptor, as does Herceptin, the two molecules are very different. The Genentech drug is a monoclonal antibody--an immune molecule hat binds to only a single target, or antigen. Monoclonals are made by cultivating antibody-producing cells in the immune system of mice, extracting them from the animals' spleen, and then going through an elaborate process to "humanize" the antibodies to avoid immune reactions in human patients.

As a protein found naturally in the body, Dimercept does not elicit similar worries about immunogenicity. But the molecule brings its own challenges. Only 20 to 30 percent of the batches made so far are usable. "It doesn't make for a good manufacturing process if you have to throw away 80 percent of the stuff," Shepard says. Receptor BioLogix's dozen or so researchers are spending much of their time giving the molecule a full makeover. As inherited from O.H.S.U., Dimercept had 13 disulfide bridges, the linkages connecting amino acids called cysteines that hang off the main backbone of the molecule. "Some disulfide bonds get mixed up during production," Shepard notes. "We're trying to redesign it to make sure that doesn't happen."

Receptor BioLogix could ultimately find itself in a face-off with Shepard's former employer and perhaps other companies that are beginning to explore similar methods of inhibiting receptors. Genentech has already initiated clinical trials for a monoclonal antibody, called Omnitarg (pertuzumab), that impedes the HER2 receptor from dimerizing with other HER receptors, possibly providing some of the same benefits expected from Dimercept in treating a range of solid tumors. Dimercept's purported benefits appear to come from hampering all HER receptors from joining in any combination. But Mark Sliwkowski, a Genentech staff scientist, says that other HER receptors prefer to partner with HER2, so inhibiting it would interfere with the others as well.

Genentech thinks its molecule has its advantages. "There's very little data about what (Dimercept) does, where it's expressed, if it's expressed, why it's expressed, what its biological role is and what its therapeutic potential is," Sliwkowski comments. All things being equal, a monoclonal antibody such as Omnitarg may be preferable to Dimercept, he notes, because it stays in the body longer and so would require smaller and less frequent doses.

Shepard was involved during the 1980s with the invention of both Herceptin and Omnitarg, the latter being one of the other antibodies that was considered early on for targeting HER2 for breast cancer. In the end, Genentech stuck with the molecule that became Herceptin. With a sense of déjà vu, Shepard remembers the long list of reasons that critics, including some at Genentech, put forward about why monoclonal antibodies might not work. Similarly, he believes that the problems confronting Dimercept may find a solution. Receptor BioLogix is working on 15 variants of the original molecule produced in Clinton's laboratory. "There are lots of ways to shorten or lengthen the half-life of a molecule," Shepard says, while adding that dimerization that does not involve HER2 is an important event in certain cancers.

Whether Omnitarg or Dimercept, the concept of preventing dimers from forming on the surface of cancer cells may prove burdensome for other reasons. Mark Pegram, a professor of medicine at

the University of California, Los Angeles, who has been contracted to test both the Receptor BioLogix and Genentech compounds, observes that both agents show promising anticancer activity in mice. The most imposing barrier to the success of these molecules as drugs, he remarks, will be development of new techniques to identify the subpopulation of patients who respond to them.

If Receptor BioLogix gets through the multitude of technical and clinical hurdles that straddle the path to an approved drug, it may have to confront its neighbor over the hill, not just in the marketplace. Receptor BioLogix's patent position is fairly strong because not many patents have been filed on proteins encoded with introns from the HER family of receptors. But if Dimercept gets nearer to market, Genentech might try to acquire rights to the drug or else come forth to defend its turf. "I suspect there's no limit to what they'll do," Clinton says. Already, at conferences, Genentech scientists have approached Clinton's colleagues and told them that they have researched variant HER proteins and that their labors led nowhere.

Worries about predations from the nearby giant are understandable. Other drugs, such as Erbitux, also interact with individual HER receptors, but none can tweak all four receptors, as Dimercept apparently does. If it works as envisaged, Dimercept, which might help patients who fall victim to a long list of solid tumors, could rake in billions of dollars of revenues a year. "The payoff is potentially huge," Shepard observes. No toxicity has been detected in mice, despite the protein's interaction with multiple receptors. The company hopes to start clinical trials in 2008. "I would say at this point, you just have to stay tuned. It's an absolutely different ball game in human trials; we won't know for a while," Clinton says.

For his part, Shepard remains in awe of the advances in molecular biology since the time he was a graduate student in the late 1970s. "Thirty years ago people weren't sure there was such a thing as receptors," he recalls. Today they name companies after them.

HOW HERCEPTIN AND DIMERCEPT DIFFER

Cancer cells often display more cell-surface receptors Of the HER family than normal cells do. When something causes receptor molecules to pair up, this "dimerization" leads the receptors to transmit signals that induce cancer cells to divide uncontrollably and metastasize. New therapies, including the breast cancer drug Herceptin and the experimental drug Dimercept, target solid tumors by hampering those signals, albeit in different wags.

DIAGRAM: HOW HERCEPTIN WORKS Herceptin is a monoclonal antibody that acts on breast cancers with a surfeit of HER2 receptors, which can dimerize with copies of themselves. Binding by Herceptin curbs signaling primarily by HER2-HER2 pairs.

DIAGRAM: HOW DIMERCEPT WORKS Dimercept inhibits both HER2 and other receptors in its family by linking to them at the site where they usually form dimers with copies of themselves or other family members. By inhibiting dimerization, this attachment can potentially prevent all known permutations of HER receptor pairs from emitting cell replication signals into cells.

PHOTO (COLOR): HALT! A new drug candidate called Dimercept, depicted in white, couples with a receptor (black) on a cancer cell and thereby inhibits signals that tell the cell to replicate.

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By Gary Stix

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