Retrotope: The Next Big Thing

Case study: Missionary
Genotype: Next Big Thing

The Challenge: When caught between a rock and a hard place, how to establish a scientific beachhead in the pharmaceutical industry with a new approach to fighting disease.

What could be better than being part of the Next Big Thing? Who wouldn’t want to have a piece of a Next Big Thing company—an Apple Amazon, Google, Netflix, or Salesforce—right on the cusp of takeoff?

Making the leap from potential Next Big Thing to actual Next Big Thing can be a particularly fraught exercise. Especially in the astronomically expensive, our-way-or-the-highway pharmaceutical arena. More often than not, researchers, scientists, and Big Pharma will have nothing to do with you or your big idea.

Retrotope Inc., a privately held clinical-stage pharmaceutical company based in Los Altos, California, faced that very problem in its goal to change aging as we know it and to put an end to the ravages of many degenerative diseases such as Parkinson’s and Alzheimer’s. To achieve that objective, the company, which was incorporated in 2006, has been advancing a revolutionary unified theory of aging and degeneration that could result in dramatically new approaches to fighting disease. It has also created a new category of drugs composed of proprietary, reinforced compounds that both treat degenerative diseases and improve quality of life as we age.
Retrotope’s disease-modifying therapy is composed of compounds that are chemically stabilized forms of essential nutrients. The company designed a new drug by making a tiny change to linoleic acid, a common and essential nutrient regularly ingested in food, after observing that the one tiny change greatly fortified cells against lipid peroxidation or the damage that cause many diseases. Because the change is so small, the body functions normally and uses the reinforced linoleic acid as it normally would—except that the cells are now “fireproofed” against the damage of degenerative diseases. In clinical tests the company has shown that when interacting with the altered linoleic acid, which is delivered in a fish-oil-like capsule, the cell membrane under assault from disease is modified to resist the damage. According to the company, the drug has limited or no side effects.

In short, Retrotope’s therapies are capable of producing monumental change in the medical and pharmaceutical fields.

Which was exactly the problem.

In addition to the fact that Retrotope’s go-to-market story was long and complicated, with its most compelling aspects buried beneath often daunting scientific terms and data, an even bigger issue was that what the company offers is both new and unfamiliar. As a result, said Dr. Harry J. Saal, chairman of Retrotope’s board of directors, it faced deep skepticism from pharmaceutical executives and investors, who viewed Retrotope as too risky a venture.

Skepticism is a barrier Next Big Thing companies often face. We’ve talked about the naysaying that surrounded Steve Jobs’ odds for success upon his 1997 return to Apple, but ridicule and scorn in the face of something new is, of course, nothing new. Henry Ford faced it down, as did one of his savvy investors, Horace Rackham, a Detroit lawyer who ignored the Michigan Savings Bank’s advice to pass on purchasing Ford stock, since, it argued, “The horse is
here to stay but the automobile is only a novelty—a fad.” And while Thomas Edison turned a blind eye to the derision that greeted his countless failed efforts (said to number in the thousands) in pursuit of his most famous invention—only to have Henry Morton of the Stevens Institute of Technology dismiss his first commercial light bulb with the prediction that it would be a “conspicuous failure,”—he himself was guilty of the very same resistance when he disparaged Nikola Tesla’s alternative power model, proclaiming that “Fooling around with alternating current is just a waste of time. Nobody will use it, ever.” And then, of course, there’s Digital Equipment Corp. founder Ken Olsen’s 1977 famous misfire: “There is no reason for any individual to have a computer in his home.”

Retrotope faced neither scorn nor ridicule; perhaps worse, no notice was paid to the new theory at all. In fact, getting a meeting with the right people at the right investment firms was proving to be a significant barrier. Without other companies doing—or at least talking about doing—something similar, it was as if Retrotope were operating in a vacuum. And (as with nature) most venture capitalists abhor a vacuum; few want to be first out of the gate when it comes to something new. “VCs don’t want to invest in an industry where there aren’t multiple companies to choose from,” said Saal. “More than one choice allows them to say, ‘OK, great, there’s a collective herd of companies attacking this problem. And it looks like maybe this one is better than that one, so here’s where I’ll invest my money.’” But when faced with just one industry option, they get cold feet. “There’s a sense that it’s just too weird, and thus too risky.”

To make matters worse, executives and investors also perceived the company’s formula—which relies on a chemical workaround that uses broad-stroke methods to counteract degenerative conditions rather than eliminating specific problems at their source, the medical research community’s preferred method when it comes to combatting disease—as threatening to
standard operating procedures, and perhaps even to careers. Which put an interesting spin on the typical Next Big Thing hurdle. Whereas Missionaries like Henry Ford, Steve Jobs, and Elon Musk likely heard (and ignored) comments like, “Don’t waste your time, it can’t be done,” what Retrotope faced was more along the lines of, “Don’t waste your time, that’s not how we do it.”

What Retrotope found, according to Dr. Robert Molinari, co-founder and CEO of the company, was that even when potential investors were interested, they quickly got caught up in the issue of what the company was doing to address the perceived cause of a specific disease, rather than what it was actually doing to avert the dysfunction. “Some people feel very strongly that you’ve got to start tackling a disease by focusing on the cause—that if you’re not doing gene therapy, for example, then you’re not curing the disease, or even fixing it,” he said.

And that meant Retrotope’s method was anything but popular. “Pick up any scientific magazine—Nature, say, or something from Stanford or any other research university—and you’ll see that the trend in modern medicine is so-called precision medicine,” said Dr. Charles Cantor, a Retrotope co-founder and National Academy of Sciences member. “That’s where you study to death a particular disease and a particular pathway and carefully engineer something that attacks that one particular pathway. Which is great. The problem, however, is that we were coming in with something that was the opposite of that. And when we talked to drug companies and told people what we were doing, right away you’d see their brows furrow as if to say, “No, no—that’s not what we do. That’s not the way we do science.’”

Retrotope, of course, was taking a different tack. Instead of working to eliminate specific diseases altogether, it was focusing its efforts on shutting down the ability of free radicals to do the damage that results in disease (not to mention aging). All diseases are a series of multiple steps, Saal explained; the question is, where along those steps do you intervene? A proponent of
precision medicine would say you should step in at the beginning—you must repair the genetic defect or otherwise prevent disease from occurring in the first place. But if you think of disease as a chain, he said, you realize that if you break any one of the links, you can break the chain. “It doesn’t matter whether you break the first link, the last link, or the middle link. If you can break a link, you stop the process.”

As an example, Molinari points to Friedreich’s ataxia, a rare neurodegenerative disease for which Retrotobe’s drug RT001 has initiated clinical trials (there are currently no approved treatments for the condition). Without intervention, patients can expect progressive loss of coordination and muscle strength, leading to motor incapacitation, the full-time use of a wheelchair, and ultimately, an early death due to cardiac complications. “If we can get patients walking, it means the disease has been modified,” said Saal. “Yes, they’ll still have the genetic defect, but it won’t have a negative impact.”

An additional benefit of the drug, at least in theory, lies in the fact that it is not Friedreich’s ataxia-specific. Unlike precision drugs, where you take a certain drug for a certain condition and it targets it perfectly, Retrotobe offers a horizontal drug, so to speak, meaning that—again, in theory—it could be used across a broad spectrum of diseases. I say “in theory” because Retrotobe, which registered its drug as a pharmaceutical rather than a dietary supplement, is bound by law to administer the drug for specified uses only, and is thus unable to suggest it for off-label use once approved by the FDA. Had Retrotobe registered the drug as a supplement, a regulatory gray zone, it would not have been subject to the same governmental approval process or rules, with consumers able to self-prescribe. But the downside to registering the formula as a supplement was the lack of serious attention that is given to the supplements industry. In many circles, supplements are seen little more than elixirs, no better than snake oil.
To illustrate the effects of a so-called horizontal drug, Saal offers anti-inflammatories as an analogy: “You take aspirin or ibuprofen for many different things, because no matter the specific disease and no matter what part of the body it affects, many diseases share inflammation as a symptom. If you have inflammation, you take a pill, and the pill you take affects your whole body. You don’t take this pill if the problem is in your stomach, that pill if it’s in your arm, and that one over there if it’s in your ankle. You dose the whole body and hopefully the inflammation subsides, even if it doesn’t necessarily fix the disease.”

Retrotope’s drug therapy works the same way in that it doesn’t matter where in the body free-radical degradation strikes. “We’re not going to have a different version for heart problems and a different version for leg problems.” And that, Saal said, is both uncomfortable and challenging for pharmaceutical companies. “They say, ‘Why are you treating the whole body when the problem is in the heart?’ The world is focused on certain approaches and we’re not doing it their way.”

As if that weren’t enough, Saal points out yet another layer of resistance Next Big Thing companies like Retrotope must overcome. “Imagine you’re a foundation that has been giving grants for research of Disease X, and for the last ten years you’ve been giving grants in order to tackle the problem a certain way. Then someone comes along with a different approach. One reaction is to say, ‘Wow, a breath of fresh air, let’s try it!’ But another, more common, reaction is to respond, ‘No, absolutely not, that’s not the way we do things, and if I go along it’s going to blow back on me.’ They’re invested in a certain worldview. Anything that challenges that worldview is not just a bad idea, it’s threatening, it threatens their career. Acknowledging that we have a viable approach is seen as denying the credibility of what they’ve been doing all along.”
As a result, when looking for partners within large drug firms, Retrotope’s proposals tended to hit a wall. “Our business development people would meet with their business development people and we’d hear, ‘Oh, it sounds really interesting. Send us the presentation deck, and we’ll circulate it inside the company.’” But that, said Saal, was nearly always the kiss of death for the proposal. Why? Because that “really interesting” deck was at some point sent for review to scientists wearing precision-medicine blinders—blinders that left them unable to absorb, much less envision, the Next Big Thing.

Retrotope also needed to overcome the perception that the company’s outside-the-box solution was too good to be true, a perception, according to Saal, that had tainted the company with the dreaded “whiff of snake oil,” The source of that whiff? A couple of things, starting with Retrotope’s unconventional story. Typically, when pharmaceutical companies conduct research, they do it in their own laboratories or pay outside labs to do it for them. Either way, the companies own the results. As a small, angel-supported company short on funds, Retrotope’s research strategy called for something different. Rather than pay to do its own research, the company manufactured limited amounts of the chemical compounds it wanted to study, and Dr. Mikhail Shchevinov, Retrotope’s cofounder and chief science officer, whom Saal calls the “idea guy,” delivered small quantities of the compound to researchers at various universities and labs around the world. (Saal also calls Shchebinov a modern day Johnny Appleseed.) Recipients were free to use the chemical for experiments in whatever study areas they chose—Parkinson’s, Alzheimer’s, Friedreich’s ataxia, diabetic retinopathies, etc.—making each research project a collaborative effort. In addition, Retrotope gained significant financial leverage by supplying only a token amount of money for the experiments, with the rest coming from grants the
individual researchers had received from the National Institute of Health, the National Science Foundation, the Parkinson’s Institute, and other organizations.

A side effect of this method, however, was that the resulting research was “all over the map,” said Saal. “While high quality, the research wasn’t designed the way a pharmaceutical company would investigate a compound; it wasn’t investigated in great depth.” Instead of initiating, say, ten experiments, all focused on one disease, Retrotepe ended up with the equivalent of one experiment for each of ten different diseases. “When we collected all our research and presented to VCs, the reaction was, ‘Wait a minute, this one compound is going to work with this and this and this?’” The answer was a resounding yes, but such results meant that Retrotepe couldn’t actually prove anything, at least not unless researchers combined data from different diseases, a process completely foreign to traditional pharmaceutical development. Which made telling its story problematic (an issue common to the world of Missionaries, where an unconventional narrative can be par for the course).

Further complicating matters was that the research also boasted data that seemed too good to be true. When Saal, who has a background in the physical sciences, first saw the data, he couldn’t believe it. “I’m used to experimental data” he said, “and when you see an effect of, say, 30 percent, your reaction is, ‘Wow! Thirty percent—that’s great! Because 30 percent is great.’” But Retrotepe was seeing results of 100 percent efficacy, which was more than great; it was remarkable. As it turns out, too remarkable, if there is such a thing, “because it appeared almost as if someone were faking the data. The numbers were just off the charts.”

An enviable problem—one any company would be happy to have—but a problem nonetheless. Retrotepe knew that in addition to finding a way to reframe the issue of an outside-the-box drug bucking the scientific norm, it needed to rid itself of that snake oil whiff.
Unlike some of the companies featured earlier, particularly our two (initially) reluctant Mothers (Tile and BuildingConnected), pinpointing Retrotone’s DNA was never a problem. It was immediately apparent to everyone involved that the company was a Next Big Thing Missionary, one that had developed a drug platform that—thanks to its ability to preserve and restore mitochondrial and cellular health in degenerative diseases—could change and enhance the lives of millions. The issue instead was how to get that message out and, at the same time, overcome baked-in resistance to the company’s raisons d’être; essentially, how to recast the company’s narrative about its disease-modifying therapy so that it would be more appealing to investors, clinical trial participants, and the press.

To that end, we first created a visionary positioning statement focused on the theory, not the drug—Retrotone is leading the advance of a revolutionary new unified theory of aging and degeneration that can result in dramatically new approaches to therapy—and then the following narrative, which now appears in some form on the company’s homepage:

Pharmaceutical startup Retrotone is changing aging as we know it so that people do not have to suffer the ravages of many degenerative diseases. The company is leading the advance of a revolutionary new unified theory of aging and degeneration that can result in dramatically new approaches to therapy—a theory based on three groundbreaking discoveries:

1) Many degenerative diseases that were originally thought to be disparate actually share a common weakness.
2) That weakness is one type of chemical bond that makes membrane fats susceptible to oxidation damage and loss of function.

3) By strengthening that bond, we are able to prevent cellular damage.

Retrotope’s category of new drugs are composed of proprietary, fortified nutrients that treat degenerative diseases and improve life as we age. Human trials of the company’s first drug have shown promise in treating Friedreich’s ataxia—a rare, neurodegenerative, and fatal genetic disease—and preclinical data support use of the drug category in major diseases such as Alzheimer’s, Parkinson’s, and diabetic retinopathies.

Untangling accessible data and messages from reams of statistics and jargon, while crucial, was just the first step. We determined that what Retrotope also needed was a story that encompassed a wide community of experts who would lend credibility to the company’s groundbreaking theories and solutions and shift attention from the company as a lone voice shouting into the wind. Remember, as noted in Chapter 4, there can be no category of one, no matter how revolutionary the Next Big Thing.

To that end, it needed experts who, despite the unconventional nature of the company’s drug therapy, would support the notion that lipid peroxidation is indeed at the heart of so many different diseases. The existence of this commonality across a wide range of diseases was not something that Retrotope should take credit for, appear to own, or defend alone. Instead, it needed to promote the message that there are other smart, credible people who view medical problems through a different lens, and who understand that there may be alternate ways to solve them. “We understood that Retrotope can’t be the only one saying these things,” said Saal. “It all
goes back to diversity of perspective. If you just try to solve problems one way—which is what the medical board is all about—you lose out on diversity of perspective.”

Recent Alzheimer’s research presents an example of that diversity of perspective, he said, pointing to studies highlighting the promise of therapeutic regimens that isolate neuroprotective agents in order to protect nerve cells from amyloid toxicity, believed to be a key player in the neurodegenerative mechanisms underlying many diseases. “Everyone has been focused on a buildup in the brain of a particular artifact of Alzheimer’s called beta amyloid,” said Saal. “Countless billions of dollars have been spent trying to solve the beta amyloid problem but they’ve had no success. And now researchers are discovering that you can have beta amyloids in the brain as long as you protect the neurons.”

The Outcome

Retrotape has been using the new narrative on its website and with investors and the press. It also organized a successful roundtable with 30 scientists representing a variety of disciplines from both universities and pharmaceutical companies to discuss ideas about a new unified theory of aging. The goal was to create momentum behind a new way to look at medical problems so that it wouldn’t feel foreign when outside-the-box companies like Retrotape set out to secure funding or partner up with foundations, research labs, universities, and other companies.

Which is exactly what Retrotape aims to do. In November 2015, the company reconfirmed its alliance with the Friedreich’s Ataxia Research Alliance and announced a partnership with the University of Florida for the opening of a clinical trial site to evaluate the safety, tolerability, pharmacokinetics, disease state, and exploratory endpoints of orally dosed RT001 in patients with Friedreich’s ataxia.
Retrotope’s strategy to penetrate the pharmaceutical industry takes advantage of the company’s broader approach to the medical world while still enabling it to maintain a focus on an orphan disease within it. Retrotope points to Friedreich’s ataxia as a specific case where it hopes its technology will reduce symptoms associated with the disease and, in so doing, suggests the potential it may offer for other neurological conditions. By providing a living example of conducting science in both old and new ways, Retrotope is inching its way toward the Holy Grail of having its drug accepted as a horizontal drug that, like aspirin, can be used to treat a variety of conditions—in this case, many of the symptoms of disease and aging.

“We don’t want this to just be a Retrotope story,” said Saal. “It needs to be a movement to look at science in a new way. Getting people together in one room makes all the difference when you’re trying to create a movement. The idea was to bring credible points of view together in a seminar setting to show that there’s momentum behind this idea of looking at medical problems in a different way. We wanted to form a group that would not only take the ball and run with it outside of ourselves, but also show that these researchers share a common vision—that they are invested in this other way of looking at the world.”

He realizes it won’t happen overnight, but what Saal envisions for the future is a brave new world of medicine in which patients can rely on a combination of therapies to treat disease, with researchers, investors, and others no longer wed to the idea that there is only one way to do things. In short, a world in which Retrotope is no longer the Next Big Thing.