FEED

Hawaii-Born Pill: The Next Wonder Drug?

BY DENNIS HOLLIER

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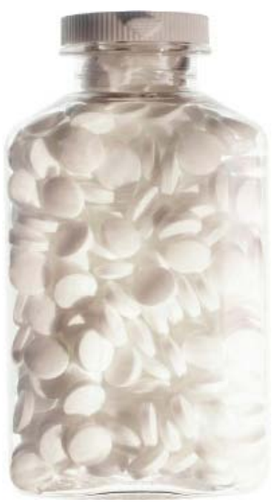
A Hawaii biotech startup has synthesized a version of astaxanthin, a drug that might become a powerful treatment for all kinds of inflammatory illnesses ranging from heart disease to diabetes. But first, the company must navigate the possibilities and challenges posed by FDA-required testing, venture capital, Big Pharma and a reverse merger. Success isn't inevitable, because, as the founder acknowledges, even good ideas can fail.



For centuries, people around the world knew that chewing on the bark of certain willow trees could ease the pain of a toothache or a migraine. By the mid-19th century, scientists in France and Germany had isolated the chemical, salicylic acid, responsible for willow bark's analgesic and anti-inflammatory qualities, but it proved too harsh on the stomach to be of real medicinal value.

Then, in 1897, a German chemist named Felix Hoffmann synthesized a purer, less irritating form of the natural compound. This new chemical, acetylsalicylic acid – better known as aspirin – became the best-selling drug of all time and is still the foundation of the multibillion-dollar corporation we now know as BayerAG.

In a modest way, a similar story may be under way in Hawaii. Twelve years ago, scientists at Cardax, a small biotech company nestled in the Manoa Innovation Center, synthesized a form of astaxanthin, a naturally occurring chemical found in shellfish and micro-algae and, like aspirin, a powerful anti-inflammatory. The natural form of astaxanthin is already a well-known dietary supplement – sometimes called a nutraceutical – believed by many to reduce the threat of heart disease. Kona-based Cyanotech, for instance, is a major manufacturer. But CDX085 – the latest in a suite of similar Cardax-patented compounds – is so much purer and more potent than natural astaxanthin, and the number of potential uses so much larger, that Cardax's team believes it may become the next billion-dollar drug. They could be right.

Despite all this promise, Cardax's path to success has been long and complicated and is far from over. Like so many startups in the life sciences in recent years, Cardax has been in a life-or-death struggle to find enough money to continue to operate.

For the company to follow the traditional developmental route for startup drug companies, investors may have to pony up more than $100 million to conduct the expensive Phase-2 and Phase-3 clinical trials necessary for FDA approval of a pharmaceutical drug. So there are still many hurdles for Cardax.

But, last April, the German pharmaceutical giant BASF finally exercised a longstanding option to become the exclusive licensee of Cardax's nutraceutical. Then, in October, Cardax announced it would use an arcane device called a reverse merger to go public. That succeeded in attracting millions of dollars in new investment for the company, setting in motion a plan to have a still unnamed nutraceutical product on the market by the end of 2014. So the company may finally have turned the corner.

All of which makes the ongoing saga of Cardax and its promising family of anti-inflammatory compounds a good introduction to the current state of biotechnology, venture capital and the evolving world of drug discovery.

Body Fights Back

To make sense of the Cardax story, you have to understand a little about inflammation. Almost all chronic diseases are inflammatory, including heart disease, osteoarthritis, diabetes and even some cancers. But inflammation itself isn't a disease. It's the body's natural response to heal damaged tissue and defend against unknown pathogens. The redness and swelling associated with an infected cut or a case of strep throat is just the body's attempt to isolate that infection and promote healing. In a tip of the hat to Celsus, the Roman encyclopedist, medical science still characterizes inflammation by the four cardinal signs: tumor, rubor, calor and dolor –swelling, redness, heat and pain. (The Greek physician Galen, no poet, added a fifth characteristic: "functio laesa" or loss of function.) Inflammation may cause discomfort, but it's an essential function of our immune system.

There are two kinds of inflammation, though. Acute inflammation, despite the name, is the normal swelling and pain associated with minor infections. Physiologically, though, it's astonishingly complex. When tissue cells are damaged, they release histamines and other chemical signals that mediate the body's inflammatory response. This causes cytokines, small proteins in the bloodstream, to induce a dilation of the veins, bringing more blood to the injury. That makes an infected cut turn red.

The dilated veins also become more porous, which allows plasma to leak through the vascular walls into the surrounding tissue. That causes swelling. Along with the plasma comes a flood of cells from the immune system called leukocytes, including bacteriophages that directly ingest bacteria, and enzymes that attack the structure of the pathogen. As the infection or injury abates, the body returns to normal. This type of acute inflammation is typically brief and effective.

But the inflammation associated with chronic disease is a different story. Rather than stem from a specific event, like a wound, chronic inflammation appears to be the result of the low-grade irritation of whole bodily systems, such as the cardiovascular system in the case of heart disease or the respiratory system in the case of asthma. Similarly, chronic inflammation isn't a reaction to a specific pathogen; rather, it seems to arise from more or less permanent stimuli, such as smoking or chemicals in the environment. That may be why diseases associated with chronic inflammation are so much more prevalent today than in the past.

Modern medicine has done a good job dealing with the infections and communicable diseases that used to be the primary causes of death. In 1850, the life expectancy of an American at birth was only 38 years – largely because of the high level of infant mortality associated with childhood diseases. But, because of the advent of antibiotics and vaccinations in the 20th century, the average life expectancy today is over 74 years. As we've begun to live longer, though, chronic diseases have overtaken infections as the leading causes of death.

It's unclear though, whether inflammation is a cause or an effect of chronic disease. "That depends," says Deepak Bhatt, executive director of cardiovascular programs at Brigham and Women's Hospital in Boston and a member of Cardax's scientific advisory board. "For arthritis, I think it's largely the cause of disease, because inflammation in the joints can cause pain, damage or even disfigurement in the joint space. In that case, an anti-inflammatory drug would be expected to directly influence the disease process. In cardiovascular disease, it's a little less clear, but I think the majority of cardiovascular experts think there's a causal relationship between inflammation and the disease, as opposed to inflammation being some kind of 'innocent by-stander' effect.

"My own feeling is it's probably a little of both. There are cases where smoking or high cholesterol, for example, can damage the inner lining of the arteries – what we call the endothelium. That can certainly lead to inflammation in the arteries and the accumulation of plaque, which can cause heart attacks. But there are also people who are exposed to all those risk factors but exhibit no signs of inflammation or cardiovascular disease. So, sometimes inflammation may be the result of cardiovascular disease, and there are cases where inflammation is the primary bad actor."

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Cardax's Compound

At the cellular level, chronic inflammation is the result of something called "oxidative stress," the buildup of an excess of molecules called "reactive oxygen species." These so-called "free radicals" are a normal product of the metabolism of cells. "Under healthy conditions, the body has ways to deal with free radicals," says Cardax CEO David Watumull. "Some reactive oxygen species are even used by the immune system to attack and kill pathogens. But with chronic disease, an excess of free radicals begins to cause inflammation and, ultimately, cellular damage."

This is what's now thought to happen in athereosclerosis, a common form of cardiovascular disease. Oxidative stress causes inflammation of the cells lining the arteries, which induces the buildup of plaque. It's plaque that causes heart attacks and strokes. Antioxidants like astaxanthin appear to provide a vehicle to remove free radicals from the cell, although the use of antioxidants to prevent disease is still controversial.

What makes Cardax's compounds differ from other antioxidants is how efficiently they work. In highly magnified X-ray diffraction images of cell membranes, it's possible to compare the antioxidant activity of Cardax's compound with other antioxidants. In a 2007 paper in the journal Biochimica et Biophysica Acta, scientists reported that they found that, while other antioxidants damage the integrity of the membrane, or provide only a partial membrane spanning, CDX085 bridges the cell membrane completely, dramatically reducing the number of free radicals inside the cell. Just as important, CDX085 appears to be incorporated in the mitochondrial membrane, the most important site for free-radical production in the cell.

This might explain the unusual effectiveness of the Cardax compounds in animal studies. Although there are plenty of anti-inflammatory drugs available today, including some of the most profitable pharmaceuticals on the market, most of these compounds can be surprisingly toxic, especially when taken in high doses or for long periods of time, as is usual for chronic disease. That's why the TV ads for pharmaceuticals, even blockbuster drugs like Lipitor or Viagra, can be so scary. On the other hand, in pre-clinical tests, the Cardax compounds appear to have had no side effects. In the industry lingo, they've shown "no known dose toxicity." If that holds true in clinical trials on humans – and, given the long history of astaxanthin as a nutraceutical, there's no reason to think it won't – this new class of anti-inflammatory drugs could treat a wide range of diseases. That's part of why Cardax looks so promising.

Then, of course, there's the size of the potential market for Cardax compounds. CDX085 was patented as a treatment of cardiovascular disease – specifically, it reduces the level of triglycerides in the bloodstream, a precursor to heart disease – but CDX085's sister compounds have been tweaked to treat osteoarthritis, diabetes, cognitive decline and other inflammatory diseases. These are all enormous markets. For example, in 2013, the pharmaceutical giant AbbVie (formerly Abbott Laboratories) sold more than $10 billion of Humira, a popular anti-inflammatory that originally targeted rheumatoid arthritis.

There's also the nutraceutical market, which includes unregulated products like vitamins, enzymes and herbal remedies that are mostly sold over the counter. Nutraceuticals have some restrictions. Because they lack FDA approval, only limited claims can be made about their uses and efficacy. This makes them less lucrative than pharmaceuticals, which can

make specific therapeutic claims. As Watumull points out, "If the FDA allows you to put 'for pain associated with osteoarthritis,' your market penetration will go way up." Nutraceuticals don't have that option. But that doesn't mean nutraceuticals are small potatoes, especially if they have a history of safe usage.

"As a dietary supplement," Watumull says, "we think the best comparison for Cardax is chondroitin/glucosamine, a nutraceutical commonly used to treat osteoarthritis. It's marginally efficacious at best, but it still sells about $2 billion a year, because it's safe. So, you have these enormous markets out there for safe anti-inflammatory drugs."

As a pharmaceutical, he says, the numbers for the Cardax compounds are even more eye-opening. "We asked the members of our scientific advisory board, a panel of unpaid medical experts who serve as independent third-party advisors, 'What percentage of your patients do you estimate would take this drug?' We thought that something like 10 percent would be great; the smallest number anyone gave us was 90 percent. They told us, 'You don't understand how desperate we are for a safe, effective treatment.' So, if you're asking, 'Who is the market for our compound?' the answer is: Anybody who has an inflammatory problem."

Venture Capital

The question is: If Cardax is such a good bet, why aren't they already a big success? The answer, as always, is money. It's expensive to be a biotech company. If you're developing a new drug, those costs can stop a company in its track. For example, the natural next step for Cardax would be to subject its compounds to human clinical trials. But Phase-2 clinical trials, usually conducted on just a couple of hundred individuals, can cost as much as $20 million. Phase-3 trials, which can involve thousands of individuals, can bring those costs to more than $100 million. "Big Pharma," the giant pharmaceutical companies that have dominated drug development for the last hundred years, will often buy or invest in companies with promising Phase-3 drugs. The Phase-2 part of drug development, though, has traditionally been funded by venture capital, and the VC world is in flux.

"They just aren't funding life sciences anymore," Watumull says. "They used to fund pre-clinical trial companies and take them through clinical trials, but they stopped doing that about five years ago to any meaningful extent." In part, he says, it's because of the risk. But it's also because of changes in their own incentives as VC funds have grown.

"Back in the 1980s and 1990s," Watumull says, "the largest funds raised like $200 million. If you're a VC, you collect 2 percent of that as your annual fee. That's just $4 million a year for expenses." Divvied up among all the fund partners, that's not a lot of profit for such a risky investment. Thus, to get the high rate of return that investors and the VCs themselves expected, they had to gamble on early-stage companies. That used to be the essence of the VC model: If you invested in 10 startups, five would fail, three would break even or make a modest profit, but one or two would be home runs and generate the 15X or 20X yields that made venture-capital investment viable. It was a numbers game.

"But, if you have $4 billion under management," Watumull says, "that 2 percent management fee is now $80 million a year. That's without doing anything. So now, VCs are less interested in investing in small, early-stage companies like Cardax. Why take the risk? Most of the companies they invest in today are Phase-3 deals."

Watumull doesn't think this is sustainable. The VC model depends on the high returns provided by those high-risk startups. If you remove the riskiest investments, you also remove most of the reward, and the returns on the less risky investments just don't justify the risk. He explains it this way: "A 7 percent upside for a successful company, against a 100 percent downside for a company that fails – that doesn't work. The amount of risk the VCs perceived was just wrong. If you wait until a company's in Phase-3 trials to invest, you have to put up at least $100 million, so there's no way you can make 10 times or 20 times on that Phase-3 company. But you can still lose 100 percent of your investment."

Watumull says this miscalculation is reflected in the recent financial performance of the major venture-capital funds. "Their returns have been mediocre at best over the past five years. That means VCs also haven't been able to raise as much money. Now, it's all going to private equity capital."

Nevertheless, Cardax tried to get VC funding. Like executives at most promising startups, Watumull and his team traveled around the country, making pitches to dozens of VC firms. Cardax even had some success, attracting interest from Ivor Royce, an icon in the VC world whose own life science companies, Hybritech (bought by Eli Lilly and Co.) and especially IDEC (merged with Biogen), more or less created the San Diego biotech community, one of the largest in the country. But the VC model had already begun its decline.

"He really wanted to do a deal with us," Watumull says. "He even gave us a term sheet, but he was unable to raise money for another VC fund. Here's a guy who'd made literally hundreds and hundreds of millions of dollars in biotech, but he was unable to do it. That was two years of our time that we spent going in the direction that he wanted to go, but it didn't lead to anything. That was very discouraging."

Cardax is far from alone in its VC woes. In fact, it's become a kind of parlor game among biotech company executives to try to explain the flaws and failures of the VC model. And, although there are signs of improvement, VC money remains tight.

Watumull cites Bill Hambrecht, the billionaire founder of Hambrecht & Quist, the investment bank that underwrote the IPOs of Apple Computer, Genentech, Adobe and Amazon: "I was at a meeting in New York where he gave the keynote speech, and he said, 'If you're a biotech company today and you are not already VC funded, the probability of you getting VC funding now is probably almost zero.' " That means biotech companies like Cardax are going to have to come up with a new mechanism to bring their drugs to market.

Big Pharma

Historically, the exit strategy for most biotechs has been Big Pharma. A company like Cardax will come up with a good product, VCs will fund its early development, then a giant pharmaceutical company like Merck, Pfizer or GlaxoSmithKline will either buy the company outright or license its technology. Even when biotech companies go public, as more than 30 did last year, they tend to partner with one of the Big Pharma companies to market their product. So, Big Pharma has always been the ultimate cash cow for emerging biotechs.

But the view is different from Big Pharma's perspective. The centerpiece of drug development for these big companies used to be their enormous research and development departments. Some of the larger companies employed tens of thousands of chemists, doctors and engineers in R&D, and for decades, these departments churned out incredibly successful drugs. Right up through the 1990s, Big Pharma was one of the most profitable industries in the country.

In the last decade or so, though, all that began to change. The R&D departments became increasingly bureaucratic and slow to develop new ideas; promising drugs that the companies invested hundreds of millions of dollars in failed in clinical trials; and, while the pipeline for new products became weaker and weaker, the patents on some of their most profitable drugs began to expire. Something had to change.

Many people, including Cardax's David Watumull, blame Big Pharma's woes on something called "targeted drug development." Instead of developing drugs from promising compounds that already exist in nature – salicylic acid, astaxanthin, curare, etc. – targeted drug development looks at the molecular pathway of a disease or a medical condition, and uses sophisticated technology to invent artificial compounds that interfere with or enhance that pathway. For example, cholesterol is produced through the regular metabolic activity of certain cells in the liver. An enzyme called HMG-CoA reductase regulates the rate of cholesterol production by binding to specific receptors on the membranes of these liver cells. Lipitor, a popular statin used to reduce blood cholesterol, works by binding to that same cellular receptor, preventing the HMG-CoA enzyme from binding there and stimulating more cholesterol production.

In other words, instead of looking at the whole animal, targeted drug development focuses on the structures of single enzymes or proteins. The idea is to create small organic molecules that either stimulate or inhibit the function of the large biological molecules in some metabolic pathway. It's all about understanding the architecture of these molecules.

Targeted drug development has been wildly successful in helping us understand how disease works at the cellular and molecular level. And, because it relies on sophisticated tools, like computer modeling and high-throughput screening techniques, this approach has also industrialized the drug-discovery process, making it faster and more efficient. But critics say targeted drug development has a fatal flaw: Because it's focused so narrowly on a single gene or a single target on a specific protein, it fails to account for how a new drug will interact with the whole body or with other systems in the body. The result, Watumull says, is an inevitable rash of side effects. "For chronic diseases, like osteoarthritis, you need systemic answers, systemic solutions."

That used to be a controversial opinion, but it's increasingly common in the biotech world. "Scientifically, targeted drug discovery is very elegant," says Deepak Bhatt. "And it makes sense in an intuitive way. But ultimately, it may not be highest yielding approach to drug development anymore."

Like Watumull, Bhatt thinks we don't know enough about how drugs work in the body. "We

do have a fairly refined understanding of the role some receptors play in the development of certain diseases. What we don't have is a refined view of what targeting that particular receptor will do to the whole system. The problem is, by antagonizing one system, there might be counter-balancing effects in another system or a couple of other systems."

While Bhatt acknowledges that targeted drug design has produced important advances in the treatment and diagnosis of some diseases ⊟notably for rare and genetic disorders – he basically agrees with Watumull: targeted drug design has hit a wall.

"The pattern of drug discovery that's evolved over the past 10 to 15 years or so," he says, "may no longer be that productive. There aren't as many blockbuster discoveries as there once were. So, maybe the approach that Cardax is espousing is a good one. If compounds like astaxanthin already exist in nature, if they're durable and there's an evolutionary reason to conserve them, that could be an appealing way to screen for different drug therapies. Certainly, that type of compound might have real appeal to patients. Patients love the idea of natural treatments."

Nevertheless, targeted development is still the dominant paradigm of drug discovery for Big Pharma. And that spills over into the VC world, where investors want to make sure the product they're selling is attractive to the pharmaceutical companies that must ultimately buy it. "These guys do tend to all run after the same stuff," said former Cardax chief medical officer Fred Pashkow, not long before he died. "VCs get enamored with the same kinds of sexy science that Big Pharma does – things like RNA interference, which affects genomic translation, or personalized medicine. They've poured a ton of money into the genomics thing that really didn't turn into any new drugs. There's been a lot of chasing after big science projects in the VC world. In my judgment, the VC model has not been working for years."

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New Paradigm

At Big Pharma companies, the response to the laggard pace of drug development has been to slash their own R&D departments. In the last five years, the industry has laid off more than 100,000 of the chemists, bio-engineers and medical doctors that it takes to run a modern drug-research program. Instead, Big Pharma is betting it can do better by buying companies that already have promising drugs in the pipeline. But, like the VC community, Big Pharma is mostly interested in products far down the development road. In effect, they've decided to pay more for their new drugs, but shift the risk of R&D to the small biotech companies.

Deepak Bhatt points out that this has major implications for how drugs are developed. "I think, in some respects, this is good for small companies like Cardax," he says, "because it creates an opportunity that really wasn't there before. That's a plus. But these small companies now also have to take things a lot further than they had to in the past. In the past, many times they would just do very basic work on a compound, and Big Pharma would take over the R&D. Now, those larger companies really want data from further along in the research continuum before they decide to invest in a compound. For small companies, that requires you to have a different set of skills. You have to be able to build things."

That's the convoluted Catch-22 Cardax is in. It needs investors to pay for clinical trials, but it needs clinical trials to attract Big Pharma investment. It has what it feels is a low-risk product, but it still doesn't match Big Pharma's risk profile.

One Big Pharma executive, speaking on background, tried to explain why a company like Cardax still looks risky to Big Pharma:

"You can't always tell if a product is going to take off or not. It's not simply a matter of being 'first to market.' Being first sometimes just means that your R&D costs are tremendous. While you're blazing a trail through the regulatory and approval process, the FDA may get worried and say, 'Increase the size of your study.' If it's a new target, they don't know what the risks are, so they may make you the guinea pig. But a company that's second or third or fourth to the market already knows the approval path. They can say, 'We don't have to do it the way Pfizer did it or the way Merck did. If the FDA made them start over and use a bigger study group, we can just start out that way.' Similarly, if the bigger study group turned out not to be necessary, the FDA may not require it for the new company. That means their costs can be lower. For example, if you look at the statin market, Lipitor wasn't first to the market; it was like fifth or sixth."

But Watumull sees the risk/reward equation differently. "We've done a significant amount of animal studies that give us confidence that the clinical studies will be successful," he says. "With target-based drug study, the risk is much higher. But the active drug in our compound is the same as in astaxanthin, so the probability of success is much higher than if the drug was coming in de novo. Certainly, using one or another of our compounds with animals, the efficacy has been very strong. That's what gives everybody here confidence. But you don't go from theory to human clinical trials without money, and the last few years it's certainly been challenging finding enough capital coming in. That's the main thing."

Finding a Path

Despite all those problems, over the last year or so, Cardax seems to have found a path to success. The key is probably its contract with BASF. Although the German chemical and Big Pharma company hasn't exactly invested in the company, it has played a key role in Cardax's development. It was BASF that figured out how to synthesize astaxanthin on an industrial scale, which means Cardax products are inexpensive to mass-produce. They're even cheaper than natural astaxanthin – cheap enough, for instance, to use as an inexpensive additive in health food products. Indeed, at one point, Cardax was in discussion with Nestle. That was only possible because of the company's relationship with BASF.

Another important development has been Cardax's decision to start with a nutraceutical, and use the income from that to develop a pharmaceutical down the road. Watumull points out that BASF wasn't always interested in expanding its relationship with Cardax. "Their change of heart came about because of the recent explosion in the global astaxanthin market," he says. "They've seen the retail market in astaxanthin go from $5 million or $10 million a year to $100 million a year. That makes somebody like BASF say, 'I've got to pay attention to astaxanthin.' "

Of course, BASF has to also be paying attention to wider anti-inflammatory market. "It's a very, very large potential market," Watumull says. "A multibillion market for osteoarthritis alone. There are probably 150 million osteoarthritis patients globally in the middle class. That's $55 billion annually, even at just a dollar a pill."

So, in a sense, the new BASF contract is just an innovative way for Cardax to adjust to Big Pharma's wary investment strategy. "We got a very attractive royalty rate on all BASF sales," Watumull says. "That's what's new. They would be responsible for all manufacturing, which we were going to pay them for, and for distribution, which we would have had to arrange for with someone else. They're also going to help with the pathway to pharmaceutical, which could have cost us $200 million." Because BASF is assuming so much of the cost of marketing and development, it will also get an exclusive license to market the Cardax product.

Reverse Merger

But the recent development that's drawn the most attention to Cardax has been its decision to go public using an uncommon technique called a reverse IPO or reverse merger.

Basically, the reverse merger is a way to take a company public without having to go through the costly and time-consuming SEC procedures. In principle, it's simple: you find a publicly traded shell company – either an existing company that's no longer in operation, or a purposely created shell –and merge your company into that one in exchange for shares in the new company. In this case, Cardax merged with Koffee Korner, a troubled Houston-based chain of coffee shops. After the merger, the new company will simply sell off its Koffee Korner assets and change its name back to Cardax. Later, it can petition the SEC to change its stock ticker symbol and it will likely be traded over the counter.

A reverse merger is one of the few ways a small company can go public. Ted Kalem, a partner with Highline Research Advisors, the investment bank handling the Cardax IPO, points out, "The classic IPO is really only possible for companies that are going to have a market capitalization of $500 million or more." That's largely constrained by rules on the various stock exchanges. For smaller companies that will be traded over the counter, a traditional IPO just isn't cost-effective. In contrast, Kalem says, the reverse IPO is probably only viable for companies that need to raise less than $15 million.

But that's the central advantage of being publicly traded: It makes your company more attractive to investors. In advance of the Cardax merger with Koffee Korner, Kalem and HRA were able to raise nearly $11 million in capital; and the mere fact of being publicly traded means it will be easier for the company to raise money in the future. "When we go public," Watumull says, "we're going to be a $100-million company. That sounds big, but it's still small for institutional investors."

Watumull also notes that the timing of the fundraising in a reverse merger is important. "What was key for me was the financing prior to the merger. With a regular IPO, all the money comes in after going public. That makes it risky. If you go through all that trouble, and something happens in the market so you can't get financing, you've wasted all that time and money. But in the case of the reverse merger, you separate the fundraising from the IPO. In this case, the company is using the imminent IPO as a way to attract investors."

But the reverse IPO isn't appropriate for all companies, Kalem says. "I think, first of all, all the companies that we work with we believe have outstanding management teams. That's especially important with the reverse merger, because it requires a lot of effort on the part of the management team to pull it off successfully. The company also has to be ready and want to be a public company, because being a public company carries certain

responsibilities that being a private company doesn't."

As an investment banker, Kalem also wants to make sure investors – who are clients, too – get a good deal. "A lot of the reverse mergers that we've done, we've taken to a retail audience. Cardax is one of them. For those, we need to make sure that the risk profile is appropriate for the retail market. There has to be a very, very low likelihood that there could be a complete disaggregation of company value. A high-risk, high-reward profile isn't appropriate for the retail investor. In our judgment, if you look at the risk profile of Cardax – given its ability to produce a nutraceutical and its contract with BASF, and the high potential on the pharmaceutical side – the risk of complete failure is fairly low."

That's an investment banker's way of saying, "This is a good deal."

But, as Watumull will readily point out, not all good ideas make it. "Not even close," he says. However, Cardax seems on the verge of a level of success that could affect not just this little biotech company and its investors, but the whole state. Watumull is one of those idealistic biotech guys who believes Hawaii can become a center for this kind of research. In that sense, he views Ivor Royce and what he did for the San Diego biotech community as a model for what Cardax could do for Hawaii.

It might seem strange to think that a modest company housed in the Manoa Innovation Center could have that big of an impact – could, in fact, have figured out problems that have stumped some of the biggest and most profitable companies in the world. Watumull, though, takes a historical view:

"Did Wang ever figure it out? Did Dell or IBM? Sometimes someone else has to come along and figure it out and supplant them. I think we can be one of those companies."

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Free radicals and Chronic inflammation

Buildup: An excessive buildup of free radicals in the human body can cause chronic inflammation. Free radicals occur naturally in the body, but cigarette smoke and pollution can produce harmful levels of free radicals.

Antioxidants: Some scientists believe that antioxidants help remove free radicals from human cells, but this remains a controversial theory.

Astaxanthin: Studies suggest Cardax's synthesized antioxidant called astaxanthin is both a very effective antioxidant and not toxic. If validated by further human tests, that would be a very attractive and uncommon combination.

Natural Sources of Antioxidants

Dark chocolate and many fruits and vegetables are considered good natural sources of antioxidants. Cardax believes astaxanthin, its synthesized antioxidant, would be even more effective than such foods in treating or preventing many chronic diseases.

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