bioentrepreneur
from bench to boardroom

Weathering a storm

Douglas Fambrough

How to handle a public relations disaster that is not of your making.

Any CEO of a life science venture must come to terms with the numerous decisions they make that ultimately turn out to be erroneous and for which they must take responsibility. But there are many other things that can go wrong with a biotech startup that are completely out of control of company management. Biotech companies—especially those working in new drug discovery—find themselves in troughs like this all the time. Such events can dramatically and quickly torpedo the business environment for your enterprise. In the following article, I describe what to do when such bad news hits your company.

The bombshell

In November 2010, I had been CEO of Dicerna Pharmaceuticals for just six months. Dicerna is an RNA interference (RNAi)-focused company I co-founded in 2007. Over my six-month period of leadership, the RNAi field had received a barrage of bad news.

Things started going south in July, when Whitehouse Station, New Jersey–based Merck announced it was shifting its RNAi therapeutics activities out of San Francisco—an ominous-sounding move, given that Merck's $1.1-billion acquisition of Sirna Therapeutics, based in Boulder, Colorado, in 2006 had helped put RNAi on the biotech map. Two months later, Novartis, based in Basel, Switzerland, ended its alliance with RNAi company Alnylam Pharmaceuticals, in Cambridge, Massachusetts. Then, in November, the big bombshell hit: Roche, also in Basel, was shutting down its RNAi flagship site in Germany, which it had acquired three years earlier in a deal with Alnylam. Roche also would sell its RNAi delivery group in Wisconsin, which it had picked up in 2008, paying $125 million to acquire Mirus Bio in Madison, Wisconsin. Having made such a recent and expensive entry into the RNAi field, Roche's decisions were a dramatic reversal for any company with RNAi technology as the core of its business.

Taken together, the announcements cast a long shadow over the RNAi field and Dicerna's business. The field was seen as having failed to make headway against its most significant challenge—the delivery of RNAi-inducing, short, double-stranded RNAs into the cytoplasm of diseased cells.

This string of negative news presented a powerful challenge to me as new CEO. The funny thing was, up until then, Dicerna had been having a very good year. Just before the Roche and Novartis announcements, I had spearheaded a $29-million venture financing round for Dicerna, putting us in a strong financial position. A few months before that, we had signed a major alliance with Kyowa Hakko Kirin, of Tokyo, and initiated a collaboration with Paris-based Ipsen. We were beginning to emerge as a force in the RNAi field.

Then, *boom*. Suddenly all anyone wanted to talk about was how the pharmaceutical industry was fleeing our sector. This perception—even if it did not completely reflect reality—had an impact on our partnering discussions, our public image and even our ability to recruit scientists and raise funds. We knew we had to plan our next moves very carefully.

The power of the meme

Public perception is not the foundation upon which real value is built in biotech. It is true that when a field is hot, you can take advantage of that perception in all kinds of ways, but you should never confuse being out of favor with lack of value. That is a lesson I had learned as a venture capitalist (**Box 1**), where staying true to the science and its commercial potential led to better investments than following prevailing trends and common wisdom. So when the Roche news broke, my first instinct was to focus on the scientific and commercial breakthroughs, trying to show the positive side of our story. When reporters called, I offered up Dicerna's successes. "Our data look good," I said, and, "We recently closed a major partnership." Or sometimes, "We're off to a great start," and, "We have plenty of money in the bank, and our investors are very bullish."

It did not work. A powerful meme—RNAi is dead—had taken hold. Whatever I said that did not fit this story line was left out.

In actual fact, the situation for RNAi in 2010 was not as bad as it sounded: Roche had indeed pulled out of RNAi, but in the cases of Novartis and Merck, it was not that simple. Novartis had *not* stopped pursuing RNAi; it had simply let a deal with Alnylam reach its natural conclusion, after having exercised both of its one-year extensions. That deal left Novartis with dozens of targets for RNAi therapeutics that it and Alnylam had jointly identified. In the case of Merck, reality diverged even further from the drumbeat of negative coverage. Merck had merely shifted its RNAi therapeutics efforts—by then encompassing more than 100 researchers—from the San Francisco campus to its West Point, Pennsylvania, facility. Yet this was wrongfully portrayed as Merck retreating from the RNAi space.

When even industry pundits and reporters cannot see through a meme to the actual facts, then there really is nothing a small company can do *at that moment*. So we went silent. This meme came along, I figured, and eventually the wave of negativity would subside. When it did, we could re-emerge and tell fresh ears that we had addressed the core issue—drug delivery. We would also have to explain *how* we had addressed the core problem and have both the data and validation for our solution. With this, we hoped, we could drive a new meme: RNAi is back.

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Box 1 My path to Dicerna

Although I was trained in genetics and the then-emerging field of genomics, I applied that training in venture capital instead of the laboratory. My scientific background was key to my decision to invest in Ribozyme Pharmaceuticals, a struggling microcap public company on the brink of bankruptcy. Ribozyme was then dabbling in the RNAi field, a technology that allows the precision knockdown of otherwise 'undruggable' genes. Ribozyme's history as an RNA chemistry company positioned us perfectly to lead this new field. Recognizing this, we refused to allow our invested capital to support the historical ribozyme work, rechristened the company as Sirna Therapeutics and moved it completely into RNAi. Four years later, Sirna became a huge investment win when Merck snapped it up in late 2006.

Even before that acquisition, I had started putting together the pieces that would become Dicerna. As a board director at Sirna, I had advocated for oncology as a rich and promising field for RNAi-based therapeutics, ripe with important yet undruggable targets, but the company had gone in a different direction. So I decided to assemble a company around a more potent approach to RNAi. This approach uses slightly longer, asymmetric double-stranded RNAs, which we term Dicer substrate RNAs (DsiRNAs). Unlike 21-mer siRNAs that are loaded into the RNA-induced silencing complex (RISC) loading complex before processing, DsiRNAs enter the RNAi pathway earlier at Dicer; this enhances incorporation into RISC and orientation for cleavage of target mRNA. When the opportunity arose in 2010 to become Dicerna's CEO, I grabbed it.

Making new champions

In this business, you are never going to win over all your critics. Even years after some technologies go mainstream, skeptics remain. For example, even after the first wave of monoclonal antibody (mAb) approvals in the late nineties, several big pharmas still had no significant mAb programs.

But we are fortunate that biotech is home to many who do not defer to the prevailing wisdom and who are instead willing to look dispassionately at the data and, when warranted, go against the grain. These are the real thought leaders, and they hold the key to coming back in any situation characterized by adverse publicity. This is the receptive audience that you need to find.

With this in mind, I resolved that when things began to thaw, I would not try to win over all the skeptics. My job at Dicerna was and is to find people who are interested and open-minded about our body of data and develop that into meaningful relationships. We want to find the folks who will look for opportunity when others are looking away. After all, we do not need everyone—we can build a great company with a small number of meaningful partnerships.

Our quiet period lasted about 12 months, during which time I assembled three things I needed to help change perceptions.

Data. Without question, the single most powerful thing a company can do to counter adversity is to solve the greatest challenges that confront it. For us and RNAi, it was drug delivery. Indeed, as soon as RNAi was discovered in higher organisms, word went out that it is a great mechanism with a big challenge: getting RNAi therapeutics inside the cell to reach their targets. Until it is solved, delivery will be seen as the Achilles' heel for an otherwise great technology. Without a doubt, challenges with RNAi drug delivery helped drive Roche's decision to exit the RNAi field.

We had already been optimizing an RNAi delivery solution when the bad news hit. During our quiet period, we let our data set snowball so we could re-emerge with a phalanx of data on our RNAi delivery technologies. We needed more and better data than what we had when the flood of bad news hit, and we were in a position to produce it.

A model. The model serves to counteract the overpowering fear that some observers bring to any discussion of RNAi therapeutics. And so when presenting our RNAi drug delivery technology and our data, it was critical that we communicate clearly and concisely the conceptual model we are following. The critical thinkers we are trying to reach do not just want to hear that there is a solution to a problem; they want to understand it.

For us, we needed to clearly explain how we have engineered our cationic lipid nanoparticle delivery system, which we call EnCore, to mediate the key steps in delivering an RNAi payload to the cytoplasm of tumor cells. There are three key steps that we call A, B and C. To successfully deliver RNA to tumors, first we need biodistribution to tumors. We call this step A (for 'accumulation'), and we take advantage of the well-known enhanced permeability and retention effect that characterizes tumor

Box 2 All for one

When Dicerna was formed, we decided to refrain from criticizing or attacking our competitors. This is a good idea for any new field, even if it is not going through a crisis in confidence. By and large, when a new biological phenomenon, such as RNAi, is discovered, several companies wind up with key pieces of intellectual property and strong investor support. When the companies in a new field attack each other, it tends to cast doubt on the field as a whole, undermining both the attacker and the attacked. The last thing we needed when re-emerging was to be our own enemy. In fact, things tend to work the opposite way, with good news for one company being good news reflected on the whole field.

We dealt with this infighting issue from the very beginning, when I had been a board director at Sirna. The first two big movers in the field, Sirna and Alnylam, sparred over intellectual property, and we easily could have been perceived by Alnylam as some sort of enemy. But we were careful to steer clear of real conflict. In fact, if you attended an RNAi conference in the years 2003–2006 when Sirna was still independent, more often than not you would have seen the senior executives of the companies relating on cordial and even friendly terms with each other. 'Co-opetition', some call it. We had enough challenges to our then small and unheralded field, so rather than tear each other down, both companies needed to put RNAi in an evermore-attractive light.

In founding Dicerna, my team and I were coming later to RNAi than Sirna or Alnylam, and as a smaller player, we wanted Alnylam to succeed because its news shapes perceptions more than anything else in the field. If Alnylam can make a success in RNAi, it is more believable that we can, too. Our story is about us having differentiating positives; it is not about someone else having negatives.

neovasculature and can be exploited through lipid nanoparticles. Our step B (binding and internalization) is gaining entry to tumor cells via receptor-mediated internalization. For some tissues, such as tumors of liver origin, our lipid nanoparticles are directly bound and internalized via tumor cell surface receptors. For other tissues, we need to engineer the binding to an internalized receptor to gain entry. Finally, we have step C (cytoplasmic release), whereby the RNAi payload is liberated from the initial internalization compartment (an endosome) into the cytoplasm. Here we take advantage of ionizable lipids in the nanoparticle that cause their fusion with the endosomal membrane, releasing the contents into the cytoplasm.

We have presented evidence at meetings that this A-B-C approach works *in vivo* (Basu, S.K. *et al.*, poster presented at the sixth annual International Liver Cancer Association Conference, Berlin, Germany, September 14–16, 2012) and has driven the engineering of our EnCore RNAi delivery system. The ultimate proof of the model and EnCore will come in the clinic, of course, which is our next major milestone.

Outside validation. While telling the world you've solved a problem is helpful, it's more powerful when you can point to outside validation for the solution. This took the form of a press release showing we had earned a $5-million success milestone from our corporate partner for excellent preclinical efficacy based on successful drug delivery. We made the press release as detailed as we could so that our success was displayed as a standalone item. There are other options for credibility, including peer-reviewed publication, but regardless, this third item is key when you again begin to talk about your story. Outside party validation is essential to getting people to pay attention.

Also, remember to keep partners and investors well-informed. They will better weather the storm with you if you provide them with a steady stream of fact-based news about your progress.

You should also take care to avoid infighting with other enterprises in your field (**Box 2**), but there was a final way in which we chose to set ourselves apart from the negative feeling around RNAi—we focused on a particular oncology indication. When we re-emerged, we made sure to link our message back to our oncology focus, as it both highlights our competitive advantage and ties directly into our solution to the core drug delivery issue. As many biotech companies have demonstrated over the years, oncology offers a wealth of opportunity to those clever enough to approach it in a new way. Effective new cancer medications command high reimbursement levels and can qualify for accelerated approvals. Those qualities, in turn, motivate big pharma to go after partnerships with small companies, sometimes aggressively. No wonder we have seen big splashes made by companies pursuing cancer stem cells (OncoMed of Redwood City, California, and Verastem of Cambridge, Massachusetts), previously unknown aspects of cancer cell metabolism (Agios of Cambridge, Massachusetts) or use of new chemistries (Avila Therapeutics, now owned by Celgene, of Summit, New Jersey).

With its RNAi technology, Dicerna can generate new first-in-class oncology therapeutics by taking well-understood 'undruggable' targets and generating drugs against them. Additionally, tumors are a tissue in which we believe we can solve the RNAi delivery problem. Although RNAi could, in principle, be used against any target, the competitive advantage of the technology lies in making drugs against undruggable targets. Some of these heretofore undruggable targets, such as MYC and the RAS family, have been understood as key oncogenic drivers for, literally, decades. They are frequently mutated, and the fact that they were originally found in tumor viruses means that evolution has already selected them as the most powerful tumor drivers. Although there is some risk that these targets will not yield the clinical impact that research suggests they should, assuming that risk is part of embracing the competitive advantage of our technology. In doing that, we are making sure that when we succeed with our technology, we will have accomplished something important. That is a message we needed the world to hear, again, when we broke our silence.

Re-emergence

In the year after the flood of bad news in the RNAi field, we assembled our data, articulated our model and generated the validation we needed to re-emerge and drive a new 'RNAi is back' meme. And it is working. New potential partners are paying attention and doing diligence, and investor interest has returned to the field. Stock prices are up. With our re-emergence, the sophisticated nature of our key audience—a few dozen pharmaceutical executives and investors, as well as clinical investigators—works in our favor. When we show them the parts and then show them that we have an answer for each part, then all they want is to see our data. That is just where we want them.

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