The Isis manifesto

Stanley T Crooke

Stan Crooke details the challenges in building a venture around an innovative platform and the implications for the industry going forward.

For more than 20 years now, I have had the privilege of leading Isis Pharmaceuticals, a company I founded in 1989 at the inception of antisense technology. I think now is an interesting time to take stock of where Isis is and what we've learned along the way.

Antisense technology still has a ways to go, but I do believe that it is now at the end of the beginning. By that I mean that based on data from several antisense drugs in the clinic (from more than 5,000 humans in our safety database) and legions of experiments in animals, I am confident that antisense drugs can be effective for a wide range of diseases.

In the following article, I detail the goals set out at the launch of Isis and how the company was built to create an innovator-supportive consortium business model that I believe is an effective approach to the discovery, development and commercialization of new therapeutics. I close by reflecting on what I feel are the most important guiding principles for creating biotech ventures capable of delivering innovative medicines.

Starting out

Before founding Isis, I had come to several conclusions that influenced the directions I have taken. First, from my time in leadership roles at SmithKline Beckman (King of Prussia, Pennsylvania; now GlaxoSmithKline) and Bristol-Myers (Princeton, New Jersey; now Bristol-Myers Squibb), I felt that research productivity in the pharmaceutical industry was declining and would continue to do so. Although the decline was blunted for some time by the product opportunities presented by the emergence of AIDS and the development of monoclonal antibodies, both of which also benefitted from very constructive regulatory

environments, most would agree today that productivity is declining.

Second, I concluded that only the creation of new, more efficient drug discovery platforms could improve productivity in a meaningful way. Creating such a platform, however, would be a significant undertaking that would require 20 years or more and a great deal of money. I felt that this could not be managed within a pharmaceutical company because of the complex agendas and investment decisions that must be made annually.

Third, I decided that the fully integrated pharmaceutical company model was not optimal for an innovation-based industry. A new business model coupled to a more efficient technology was needed. This is what spurred the opportunity for Isis.

The Isis model

So why antisense? After considering several technologies, I concluded that antisense had the highest probability of success, that it could have the broadest applicability and that it had the potential to greatly increase drug discovery productivity. I felt antisense would be a medicinal chemistry-based pharmacological technology that conceptually could be used for virtually any disease, except single-gene deficiency states. Moreover, based on the size and physicochemical properties of first-generation antisense drugs, I believed that I could predict their behavior *in vivo* reasonably well. Finally, I felt that antisense technology could improve the productivity of drug discovery and early development. The central reason for the inefficiency and lack of predictability of traditional drug discovery and early development is summed up by the old adage, "Change a methyl, change the drug."

Although drug discovery is more sophisticated today than ever before and some general principles can be applied, the adage remains appropriate. We also still have a limited under-

standing of the forces that determine selective affinity for one protein receptor over all other proteins. At the early development stage, every new drug behaves differently, so we can't learn much from past experience to lower the failure rates in early development. Across the drug industry, the most effective response to this set of problems has been to increase scale (that is, increase the shots on goal). Unfortunately scale has been shown to yield diminishing returns largely because of the negative impact of size on innovation.

With antisense drugs, we understand the forces that result in binding selectively to RNA receptors (Watson-Crick base pairing), so antisense-based drug discovery has proved to be much more efficient and less costly than traditional drug discovery. Because members of the same chemical class of antisense drugs have the same basic properties, my experience is that their behavior has proved to be more predictable than that of small molecules, resulting in a lower failure rate in early development. These factors coupled with shared manufacturing and analytical and formulation processes result in dramatic improvements in efficiency.

Knowing all this, my original idea for founding Isis was that truly innovative drugs, ideas and people are rare and must be protected, encouraged and developed. Typically, anything that doesn't contribute directly to innovation destroys it. The model created at Isis is thus based on two fundamental concepts.

First, to create and expand the technology platform, build a company that is highly innovative and structured to maximize multidisciplinary problem solving. The organization needs to be nimble and collaborative. It needs to apply academic rigor while remaining focused on tangible output. Second, build a business model that maximally exploits the technology without creating cumbersome infrastructure that could be a drag on innovation.

Stanley T. Crooke is CEO and chairman at Isis Pharmaceuticals, Carlsbad, California, USA.
e-mail: scrooke@isisph.com

The result is the creation of a highly innovative research and drug discovery company. Isis is one of the largest patent holders in the biotech industry, and we have an impressive inventiveness rate per employee. For example, a 2011 patent survey by The Patent Board ranked Isis as the fifth innovator on its biotech industry scorecard, behind larger firms such as Johnson & Johnson (New Brunswick, New Jersey) and Roche (Basel, Switzerland).

The first part of our strategy in creating Isis was to combine all of the new disciplines—oligonucleotide medicinal chemistry, RNA receptor biology and nucleic acid analytical methods—necessary to tackle the antisense problem in an environment in which scientists would work together toward a common goal. The two keys here were to keep the organization small and focused and to tolerate as few structural impediments to innovation as possible. In other words, keep it simple.

The second part of the strategy was to ensure that the innovations of the core team were fully exploited. This required that Isis be highly collaborative, a concept that was and still is an anathema to many technology owners. The company's partners had to do three key things: work with us in expanding the technology platform, take drugs beyond early development to the market and work on drugs outside Isis' main areas of therapeutic focus.

Working with companies and academic collaborators outside of Isis allowed the overall effort to receive the benefit of many more brains, hands and dollars to move inventions forward. Since being founded, Isis has worked with established companies and formed several satellite companies to work on specific opportunities. The notion is to create a consortium that can say yes to opportunities but does not prevent the emergence of new ideas or drugs.

Guidelines for success

My experience in leading Isis through the aforementioned challenges and other developments has led me to form several guiding principles, which I describe in more detail below.

Do something worthwhile. Dream big. Why dream small? Great achievements occur when great leaders create galvanic visions and lead well-managed organizations toward those visions. Nearly everyone I have known wants to be a part of something bigger than themselves. Such a dream properly described and implemented is captivating and can be used to recruit others who share your dream.

The truth is, though, that I worry dreaming big and realizing those dreams is harder today than ever before. In fact, I wonder if the research-based drug discovery industry can remain vibrant. Certainly, the industry today

faces the most daunting challenges that I have seen over my entire career.

First off, the tasks are harder. Most acute and infectious diseases (which are intrinsically easier and less costly targets for drug development) that affect the developed world are effectively treated in most patients. Also, for most chronic conditions there are agents that ease symptoms and slow the progression of the disease, so today virtually all new agents must enter development to be *used in combination with* or must be shown to be *better than* existing agents.

This is a very difficult challenge, and it means that for a great number of opportunities, risky and costly outcome studies are required for approval. It can be cost prohibitive for even the largest companies to simultaneously develop several drugs requiring outcome studies. That puts pressure on innovation, and companies then are less able and willing to take risks on new therapies.

This is all compounded by a very risk-adverse regulatory environment and by dwindling effective periods of exclusivity. These elements raise the sale price of new drugs, even as payers are imposing pressure to lower prices.

This raises an interesting question: Would Isis be financeable today? The concern is less related to startup financing and more to the ability to raise public equity and to develop the large company partnerships sufficient to support such an enterprise. I think it would be substantially harder today than it was in 1989. (Of course, funding Isis for 20 years hasn't been a walk in the park either.)

But in truth, I am more concerned about the lack of big ideas across the industry. Where are the big ideas of today? Where will new ones come from if most entrepreneurs are pursuing the more easily understood and financeable circumscribed opportunities?

Prepare to persevere; prepare to call it a day.

By definition the bigger the idea, the harder the task, the longer the timeline to success and the higher the probability of failure. If you have committed to solving a big problem and you are making sufficient progress to convince yourself that the technology is likely to work, you will need to rally your supporters and persevere despite the naysayers.

You also have to be prepared to admit defeat. On a few occasions, Isis has been confronted with disappointments and challenges and has considered accepting defeat or changing direction. However, based on a thorough critical review of all the data, the company's leadership concluded that despite the setbacks, continued investment was justified. I was, however, always ready to make a negative decision if

the data failed to support the technology. There is a fine line between data-based perseverance and irrational, emotionally based obsession.

Prospectively identify issues; invest to understand them. When Isis was founded, I believed that many potential side effects of antisense could be predicted based on its physicochemical properties. From day one, the Isis team developed experimental systems to characterize these risks and understand the molecular mechanisms that were responsible. When starting a company, you must recognize that potential problems exist; if you don't invest early and consistently, they will become emergencies.

Obviously, it is not possible to foresee every problem or to predict clinical trial outcomes or changes in the regulatory environment, but you must be ready to respond to unexpected results and challenges. Too often biotech leaders don't identify problems prospectively. Instead, they ignore them. That is simply an unacceptably risky strategy.

Build and retain a strong, cohesive team. You must have a team that shares your vision and commitment. Isis has always been an intense, demanding environment, yet the company has invested heavily in nurturing and growing leaders internally. Moreover, I felt that the company had to keep turnover low so that the corporate memory was preserved as the enterprise grew. Our voluntary turnover rate has averaged about 3%, and many junior and senior people have been with the company for 20 years or more. To assure new people and new ideas are brought in, the company has a very successful postdoctoral program. You'll need to decide what sort of organization you need to meet the awaiting challenges and manage the processes that affect the company as aggressively as you manage financing, partnering and drug discovery and development.

The more unique the company culture, the greater the challenge in creating and maintaining a cohesive senior leadership team. You must accept that you will make mistakes (I certainly have made my share). But when your gut tells you that you have made an error, act immediately. There are always many reasons to temporize, but my experience is that the longer you wait, the worse the situation gets.

It is also important to create a strong and unified identity or culture for the company. At Isis, three central tenets are at the heart of our culture: commitment to the patient, commitment to science and commitment to outstanding leaders. All the processes and systems in the company are geared toward supporting those three ideals. Because inno-

vative leaders usually have quirks, the view at Isis is to have as much tolerance for individual behaviors as possible and as few rules as possible. Those decisions that can be decentralized are, and people are given the opportunity to succeed with as few impediments as possible. The heart of the company is centered in Thursday data clubs, in which all scientists present their work as it progresses. Also, program reviews evaluate the progress in each program once a year. I don't think that I have ever missed a program review.

Isis invests extensively in communicating with all of its employees. You can't expect people to really commit to a vision unless you share the vision with them and trust them with as much information as possible. As a result the company has frequent all-employee meetings and informal meetings between small groups with members of the senior leadership team. I also use the e-mail and intranet system to have 'fireside chats' to update everyone on various projects. Everyone is encouraged to understand how decisions are being made, and employees are trusted to deal appropriately with good and bad news alike.

In fact, when you experience failure, communicate carefully and explicitly. Isis has had two major phase 3 failures with first-generation antisense drugs: alicaforsen (ISIS-2302; AP 1007) and Affinitak (aprinocarsen). It was painful to disclose those disappointments and even more difficult to deal with the after-math, including negative investor sentiment and layoffs. Nevertheless, I think the fact that management dealt with those disappointments as forthrightly and honestly as possible preserved credibility and created the opportunity to continue the endeavor.

Partner often and flexibly. You will not be able to raise all the funding you need in the equity markets, so research collaborations are key.

Moreover, partnerships make intellectual contributions and add rigor to processes. Exciting ideas will generate critical early adopters. Within the first few months of founding Isis, three research partnerships were concluded with early adopters. The largest, longest lasting and most important was with Ciba (Basel, Switzerland; now a part of Novartis). Later on, an even larger partnership was completed with Eli Lilly (Indianapolis). That relationship was also seminally important to the evolution of antisense technology and Isis. As Isis has grown into a more mature company, the management has become more selective about the types of partnerships entered into; even so, many of the company's accomplishments could not have been achieved without the many partnerships that were forged as the enterprise grew.

Partnerships also end. Sometimes they end with success, other times, disappointment. You must understand that your partners have complex agendas and other issues that influence investment decisions. Thus, it is likely that some long-term, technology-based partnerships will end before achievement of the ultimate goals. Prepare for those events. Usually, they result in temporary disruptions and depression of stock prices, but you can typically take what has been accomplished, build on it and partner again.

Plan and invest for success. Success is never easy or cheap. You must invest time and money. You cannot create a new future unless you invest consistently in it. In practical terms, this means dealing with today's problems using existing technology while investing in longer-term solutions and advances. This is often not easy to explain to investors. It also means that when you experience disappointments and need to take difficult actions, such as layoffs, you manage those as elegantly as possible.

Isis has had to impose two layoffs during its history. I think these were handled professionally and compassionately, and much effort was invested in communicating with our employees. Consequently, the damage done to morale was minimal and temporary, and many of the people who were laid off have been rehired. That would not have been possible had company management not behaved responsibly.

Create and lead a committed, effective board.

You do this by recruiting people who want to see your dreams realized and by treating them like full partners. This means that you provide clear and consistent communication about company successes and failures. It means that you spend the necessary time to assure that board meetings are decision oriented and focused on the key strategic issues. Your board has responsibilities that differ from management, but they must be full partners or they won't be there when you need them.

Conclusions

There are many ways that one can look at Isis. For me, it has been a 20-year experiment in a new technology and a new type of business model. It has certainly been an interesting journey that has provided many lessons and taught me a lot. There remains plenty of work still to do, and the company has yet to provide the great return to our shareholders or patients that I hoped it would—the company continues to work toward that set of goals.

For years, I have been fond of saying that I have encountered only two tasks that were really difficult, and both are often dismissed by those who haven't tried them: being a good parent and making new drugs. I think I can now add a third: creating a new platform for drug discovery and development. All three are well worth the effort.