



Steven Holtzman discusses partnering

Interviewed by Rebecca N. Lawrence

Steven Holtzman, Advisor to the CEO, Millennium Pharmaceuticals; and Chairman and CEO, Infinity Pharmaceuticals

What do you think were the key events that made Millennium's growth so successful?

The most important thing for Millennium was that from the beginning, it was recognized that the key to building a successful and great company is hiring great people and providing an environment in which great people can do great things, both as individuals and as members of a team. One can point to other events such as the partnering, but the partnering would not have happened but for the fact that there was an incredible group of scientists and business people working together to build something very special. The partners recognized this and therefore realized the need and desire to tap into it.

Do you think partnering is essential to the growth of both biotech and pharma companies?

If we are talking about biotech companies as companies that are taking fundamental discovery technologies and attempting to develop new drugs from them, then I think partnering is absolutely essential. As biotech companies will not have products that generate revenues for the better part of a decade, unless you are going to finance the enterprise entirely with equity and equity-type investments, you need to be able to sell something. Partnering is about selling intermediaries along the way to drugs while you are in the process of producing drugs for yourself that will provide the revenues you need to enable your company to grow. The key to this is using partnering to generate the necessary current revenues to grow and yet ensure that your company retains significant assets in the way of knowledge and product rights so that you can develop products yourself and further forward integrate up the value chain.

From the perspective of the pharma industry, partnering is the way to tap into cutting-edge early-phase new discovery technologies.

Do you see such collaborations increasing in the future?

I think they will continue as they have always been an essential part of this industry. Certainly, the major pharma companies are likely to continue to increase outsourcing the earlier phases of drug discovery. The climate is one that is more receptive to alliance relationships that also acknowledge the needs of the young company and not merely as a means to deliver something to the pharma company.

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What are the major pitfalls and benefits of such collaborations for each side?

Agreements and alliances come in different forms. There is a fundamental divide between transactions and relationships. Transactions involve the exchange of goods or services for a payment and then the transaction is over. It is well defined up-front and both parties have to enter this with an understanding that there is a mutual benefit for a limited duration. Here, it is perfectly reasonable and consistent with the values of the marketplace for both parties to try to get the best deal.

By contrast, a relationship will definitely have stated goals but will be for a longer duration and generally broader in nature such that you know that you will not envisage at the onset all that you can produce. Consequently, you need to be going in with the attitude that things will go wrong and opportunities will arise in ways that you did not anticipate. The relationship should therefore be structured as an ongoing dialogue so that problems can be openly acknowledged as well as new opportunities identified.

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The major pitfall is to mistake a relationship for a transaction. There can be multiple reasons for this happening. Often, in the course of the relationship, the players change. If the relationship is structured around key individuals and these individuals change, the new people coming in will not necessarily have a sense of ownership of the relationship and that can result in the new people viewing it as a transaction. The question then becomes how to structure the relationship so that, while it has to be built around human beings, it also has structural features that create a relationship between the organizations/institutions. This means that, if and when there is a change of players, there is sufficient institutional commitment to the relationship that the new players are brought in with the expectation of being initiated into and taking ownership of the relationship. Other problems can be a change in the goals of the corporations involved where it sometimes makes no sense to continue a relationship.

What do you think are the essential ingredients to make a collaboration work?

If it is a large collaboration, the most important ingredient is that the object of the relationship is something that is very important to both companies, even if it is for different reasons. The second ingredient is that while there is alignment in respect of the goals, what the companies might wish to achieve from the relationship aside from those goals could be different. For the young company, the relationship might be not only developing this particular product but also building the company. However, for the pharma company, it may be simply adding the product to its portfolio.

Each company's individual environment, and therefore the role of its original goal, might change. However, it might change for one partner but not for the other so it is important to remain conscious of what the other players' goals are: if you are seeking a change in the relationship because of changes in your own environment, you need to walk a mile in the other guy's shoes first. This is very important because if your main goals become inconsistent with the broader goals of the other company, even though the narrow goals seem to be the same, then the relationship is not going to be successful.

How has Millennium used partnering to build on its capabilities and how did its strategies evolve?

In the early days of the company, the goals of Millennium were to validate the technology as well as to provide the financial stability necessary to start to build the company. It was also important at this stage to build our knowledge and capability bases so that we could begin to forward and horizontally integrate into new areas to expand our base. As that became successful, the nature of the relationships we needed changed: we had to have more participation in the later phases of discovery and development so that we could participate in the greater value gained from the product.

You need to think of it in the same manner as you would develop an investment portfolio where, in the early days, you have less ability to take financial risk. Over time, the nature of the primary risk changes from financial risk to partner risk because, no matter how good the relationship is with your partner, you are two distinct companies and your environments and goals can change independently of each other. Hence, total reliance on a partner for the future of your company is not a good idea. In the early days of a company, it often seems as if you are almost forced into such partnerships. This way of thinking must be avoided. Rather, these relationships should be viewed as ladders that you are using to get to a stable place from which you can go into the future.

What kind of technology infrastructure has Millennium built up and how does this impact on which companies to collaborate with?

I think there have been a few technological revolutions in the past couple of decades

where a couple of companies have recognized them and jumped on them. One was obviously the recombinant DNA revolution of the late-1970s/early-1980s. In the early to mid-1990s, genomics was another such revolution that had the ability not simply to fill up various fields with potential drug candidates but rather to change fundamentally the nature of the discovery enterprise.

It all begins with the science – you are not going to be a preferred partner if you do not have world-class science.

Millennium and its founders recognized this genomics revolution and so, in terms of the technology in the early days, the key was to put in place the genetics and genomics technology and scientific platforms that big pharma did not have at this time (it must be remembered that big pharma did very little early-stage biology and arguably still does). We then effectively saw the need for the pharma industry to move backwards into early-stage biology. The platforms that were put in place were therefore broad-spectrum genomics and genetics technologies: DNA sequencing, genotyping, high-throughput means of looking at transcriptional differences, and the informatics infrastructure. This allowed for a series of partnerships where corporations were looking to tap into the applications that had arisen from our work, either through buying the applications or through technology transfer.

That can sound as if Millennium was a tool supplier but in fact we never supplied or sold tools. Rather, we transferred overall discovery systems where we had taken those various tools and integrated them, bound them together using proprietary informatics, and developed Standard Operating Procedures to produce a process that yielded results. Consequently, we entered into several relationships where, in addition to (or independent of) working with a partner to identify drug leads/targets, we actually transferred the technology so that they could use it broadly in their own company. I think the crucial thing for us was the recognition that our success as a company would come from our own application of the technology whether alone or in collaboration and so transferring the technology to others to exploit our

platforms was not inconsistent with our overall mission.

How does Millennium build its reputation as a preferred partner?

It all begins with the science – you are not going to be a preferred partner if you do not have world-class science. Once you have established relationships, it is a small world and people essentially reference you with your own existing partners. The most important things are then whether you have a reputation for integrity and that, when you enter into a relationship or partnership, you really strive to have open dialogue and live-up to your commitments in so far as you can. The fact is that the nature of drug discovery is that you are going to fail more often than you succeed so all one can expect from each other is your best effort and acknowledgement when things are working and when they are not. You also must keep moving ahead with your technology platforms and not get frozen. Although you might be a preferred partner today, it does not mean you will be tomorrow.

How do you select the best groups to partner with?

We have found that it is less important to get together with the perceived leader than a lot of people would seem to say. Often, the person who is 'number 2' but is hell-bent on being 'number 1' might be a better partner than the guy who is already 'number 1' and therefore could become complacent. Another key point is that while corporations develop overall reputations, we all know that excellence resides locally: what comes from the top is culture, attitude and integrity but there can be local centers of excellence. It can therefore appear that you are getting together with a group that is not the best but locally they have an enormous commitment and excellence. Finally, in a large relationship, it is important to be needed and not just wanted: you should find a partner that has complementary excellence but is weak where you are strong.

What has been Millennium's most successful partnership and why?

There have been so many of them and success has been different in different ways. I can think of ones that did not work as well as we would have liked or that worked out probably not as well as the partner would have liked. The ones that

stand out are probably some of the bigger ones where the goal was incredibly audacious and we still managed to deliver on it.

For example, we have a very large relationship to transfer a whole technology platform to Monsanto and help them establish an agricultural genomics subsidiary, Cereon, in Cambridge (MA, USA). To succeed in starting a company from scratch that was Monsanto-owned but that had the culture of Millennium and be up and running with a full genomics platform in three months was extraordinary but I think we succeeded because both companies were extraordinarily committed. The program with Bayer has also been extraordinarily successful: again, we set a very audacious goal to deliver a huge number of targets in a broad range of diseases. Maybe the general lesson is that the more important the success of the relationship is to both corporations, the more likely it is to succeed because there is more at stake and so people cannot afford to be petty.

In the pharma industry we still operate too much in a world of silos.

What advice would you give biotech companies to make themselves more appealing to pharma companies for collaborations?

Have absolute, impeccable quality science, interact with absolute integrity, recognize whether what you have addresses an important need of the partner and don't try to force fit it if it doesn't.

Do you think that companies that try to 'go it alone' or are reluctant to enter into such collaborations can still be successful?

With respect to biotech companies, I would say yes, in the short term. If in fact the discovery you have made is a billion-plus-dollar product with a five-year development-cycle-to-market that addresses an incredible unmet need then don't partner! If on the other hand, that drug candidate fails, you are going to have a lot of problems. People often point to Amgen as the example of the successful company that did not partner but the fact of the matter is that partnering was essential to Amgen's growth. However,

what they did was retain significant rights for their own exploitation of EPO and GCSF.

What new or alternative approaches do you think biotech/pharma companies can use to enable them to significantly increase productivity?

The most important thing for increasing productivity is knowledge integration and dissemination. There is an enormous amount of information and data being generated around the world and it is more than the human mind can absorb. Consequently, there must be significant investment in systems that enable the capture and integration of that information and presentation to scientists and managers so as to maximize its value. The second way to improve productivity is organizational: in the pharma industry we still operate too much in a world of silos. Consequently, there is an enormous amount of productivity improvement that can come from better attention to processing and organizing communication among team members. The third point is a need for a culture that rewards killing projects – a lot of failure in productivity results from projects living longer than they should. Fourth is that companies need to focus – if you go through any company, there is usually a portfolio of hundreds of projects, each of which has say 0.3 FTEs (full-time employees) – this adds up to a lot of heat and very little light.

Increasingly, many biotech companies are trying to convert themselves into pharma companies – do you think this is an appropriate move for all types of biotech companies?

If you go back to the early-1990s, we had the crash-and-burn of several major companies trying to develop drugs (e.g. the Synergens of the world and the failure of Centocor's Centoxin). This led to the preferred model of the mid-1990s of companies that generate lots of current revenues from selling technologies and product rights. Now we are seeing a reversion to the fundamental understanding that in order to generate significant financial valuation, you have to participate in drug discovery, development and marketing all the way up the value chain.

If you start with a piece of software or screening technology and decide to fully integrate to become a drug discovery company then I suppose it is possible but it

means you will need to add chemistry, biology, pharmacology, physiology, ADME/tox, clinical development, and so on. That is no mean task. The main question is what advantage do you have in that respect and is it sufficient to provide the necessary leverage. You can take the example of Celera, which has recently announced that, in addition to being a database company, it is going to use the information itself and become a drug discovery and development company. Celera has the advantage of a billion-plus dollars in the bank which will enable them to forward integrate through acquisition. Most companies do not have that luxury and, in any event, the challenges remain huge. Whether it will be done successfully, at the end of the day, is a function of whether they succeed in developing the drugs.

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Where do you see the industry in 20 years time?

If one looks at the history of the automobile industry, it is of course a striking fact that there were dozens if not hundreds of car-manufacturers in the early part of the 20th century and today we have essentially 8–10 of them. Hence, seeing further consolidation in the pharma industry would not be surprising. I think that we will start to see a better generation of medicines emerging that are based on a discovery and development process that is more closely coupled to understanding the biological basis of disease and the nature of the subject at a molecular level so that drugs can become more tailored. I do not know whether that really means a whole bunch of personalized niche medicines because I think one can bring the understanding of the disease back into the discovery process and in some instances, produce drugs that cut across molecularly distinct populations. However, I think we will see better medicines that are more closely coupled with an understanding of the subject's state.

What are your main worries or concerns about the industry?

My main worry is that in western society, we have assigned to the for-profit industry the role of developing medicines when, in some fundamental sense, people view medicines and health as an entitlement and not as goods to be bought and sold on the marketplace. Consequently, there is an intrinsic tension between the moral desire for universally available good healthcare and the needs of the industry to continue to generate growth and profits. The industry needs to take a very enlightened perspective on issues such as the availability of medicines to developing nations and the provision of government-sponsored healthcare. The industry needs to work collaboratively with governments and non-governmental organizations rather than fight each other to decide how we are going to do this in a manner that serves that greater end. This requires

engendering a longer-term perspective of a kind of partnership.

I understand you have just left Millennium. What are you planning to do next?

Chairman and CEO of a new start-up drug discovery company based in the Boston area called Infinity Pharmaceuticals, which will be getting going in the fall of this year.

What would you like to have achieved by the end of your career?

I would like to have participated in helping to build one or more companies that develop important new medicines and which are social organizations that themselves encourage creativity. I have had the great fortune of working with Mark Levin to help make this wish come true at Millennium. If I am fortunate, Infinity Pharmaceuticals will provide the opportunity to do it one more time.

I also have a deep interest in public policy and bioethics. By the end of my career, I would like to have contributed to the creation of a life sciences industry that takes seriously our social responsibility to ensure that our technologies are used broadly for the benefit of as many people as possible. To make this happen, it will need to be an industry that engages constructively with the public and the public's representatives to make it more likely that we figure our way through that basic dilemma of how do we have a profitable industry that simultaneously provides goods that are fundamentally an entitlement.

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Do YOU think partnering is essential to the growth of both biotech and pharma companies?

What new or alternative approaches do you think biotech/pharma companies can use to enable them to significantly increase productivity?

Where do you see the industry in 20 years time?

Please send your comments to Dr Rebecca Lawrence, News & Features Editor, *Drug Discovery Today*

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